RELATION BETWEEN HYPOTHYROIDISM AND NON-ALCOHOLIC FATTY LIVER DISEASE

Submitted in partial fulfilment of Requirements for

M.D. DEGREE BRANCH I

GENERAL MEDICINE

OF

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI

INSTITUTE OF INTERNAL MEDICINE

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CERTIFICATE

This is to certify that the dissertation entitled **"RELATION BETWEEN HYPOTHYROIDISM AND NON-ALCOHOLIC FATTY LIVER DISEASE"** is a bonafide work done by **Dr.A.DINESH**, at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations forward **of M.D Degree in General Medicine (Branch-I)** under our guidance and supervision during the academic year 2015 -2018.

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I solemnly declare that this dissertation entitled "**RELATION BETWEEN HYPOTHYROIDISM AND NON-ALCOHOLIC FATTY LIVER DISEASE**" was done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during 2015-2018 under the guidance and supervision of my chief **Prof.Dr.G.SUNDARAMURTHY, M.D**. This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of **M.D. Degree in General Medicine (Branch-I).**

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ACKNOWLEDGEMENT

At the outset, I thank **Prof.Dr.R.NARAYANA BABU M.D., DCH**, Dean, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 for having permitted me to use hospital data for the study.

I am grateful to **Prof.Dr.S.MAYILVAHANAN, M.D**., Director and Professor, Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3.

I am indebted to **Prof.Dr.G.SUNDARAMURTHY, M.D**., Professor of Medicine, Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 for his valuable guidance.

I would like to thank **DR.T.S.KARTHIGEYAN M.D and DR.B.RAMESH M.D**, Assistant Professors, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 for their scrutiny.

I would also like to thank **PROF.Dr.K.NARAYANASAMY**, **M.D., D.M.,** Head of the department of HEPATOLOGY for his continuous support and expert guidance.

I express my sincere gratitude to all the patients who participated in the study.

Lastly, I thank all my professional colleagues for their support and valuable criticism.

ABBREVIATIONS

ABG	-	ARTERIAL BLOOD GAS ANALYSIS
BMI	-	BODY MASS INDEX
BMR	-	BASAL METABOLIC RATE
CCF	-	CONGESTIVE CARDIAC FAILURE
CVA	-	CEREBRO VASCULAR ACCIDENT
DIT	-	DIIODO TYROSINE
ELF	-	ENHANCED LIVER FIBROSIS
EOI	-	ENZYME LINKED HYPOIODATE
ER	-	ENDOPLAMIC RETICULAM
FDG PET	-	FLURO DEOXY GLUGOSE POSITRON EMISSION TOMOGRAPHY
FGF	-	FIBROBLAST GROWTH FACTOR
FNAC	-	FINE NEEDLE ASPIRATION CYTOLOGY
HAART	-	HIGHLY ACTIVE ANTIRETROVIRAL THERAPY
HCC	-	HEPATOCELLULAR CARCINOMA

HOI	-	HYPOIODOUS ACID
IBD	-	INFLAMATORY BOWEL DISEASE
LDL	-	LOW DENSITY LIPOPROTEIN
MI	-	MYOCARDIAL INFARCTION
MIT	-	MONOIODO TYROSINE
MRE	-	MAGNETIC RESONANCE ELASTOGRAPHY
NAFLD	-	NON-ALCOHOLIC FATTY LIVER DISEASE
NASH	-	NON-ALCOHOLIC STEATO HEPATITIS
NHANES	-	NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY
NNFL	-	NON NASH FATTY LIVER
NSAIDs	-	NONSTEROIDAL ANTIINFLAMATORY DRUGS
PBI	-	PROTEIN BOUND IODINE
PPAR	-	PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR
TNF	-	TUMOUR NECROSIS FACTOR

RAIU	-	RADIO ACTIVE IODINE UPTAKE
T3	-	TRIIODOTHYRONINE
T4	-	TETRAIODOTHYRONINE
TBG	-	THYROID BINDING GLOBULIN
TFT	-	THYROID FUNTION TEST
Tg	-	THYROGLOBULIN
TPN	-	TOTAL PARENTRAL NUTRITION
TPO	-	THYROID PEROXIDASE
TRH	-	THYROID RELEASING HORMONE
TSH	-	THYROID STIMULATING HORMONE
UDCA	-	URSODEOXYCHOLIC ACID
VLDL	-	VERY LOW DENSITY LIPOPROTEIN

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INTRODUCTION

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) represents a broad clinical spectrum ranging from simple steatosis to nonalcoholic steatoheaptitis (NASH), which may progress to liver fibrosis, cirrhosis and hepatocellular carcinoma.[1] NAFLD is a rapidly growing diagnosis and it is the most common cause for abnormal liver function test worldwide.[2] The growing pattern of NAFLD prevalence is generally attributed to a global increase in the prevalence of obesity and other metabolic risk factors[3]. Advanced age and metabolic disorders like Type 2 diabetes, impaired glucose tolerance, and central obesity are among the risk factors for NAFLD.[4,5,6] Cryptogenic cirrhosis is a term used for those patients with liver cirrhosis who lack any identifiable viral, alcoholic, autoimmune or drug related cause of the condition. Many clinicians now believe that a considerable number of these patients have cirrhosis due to NASH.[7] NAFLD incidence increasing especially in developed and developing countries, it is anticipated that cirrhosis due to these conditions may surpass other causes of cirrhosis in a near future. Therefore understanding the pathophysiology risk factors and new treatment options of NAFLD should be among the priorities in the field of hepatology.

Endocrine hormones are generally involved in cell metabolism, regulation of energy expenditure and fat distribution in the human body and thereby play an important role in the development of metabolic abnormalities. The thyroid gland is significantly involved in energy homeostasis, lipid and carbohydrate metabolism, regulation of body weight and adipogenesis.[8,9] In a clinical setting, subclinical hypothyroidism has been associated with metabolic syndrome, cardiovascular mortality and disturbance of lipid metabolism[10,11]. In recent years, growing body of evidence has led to speculation on the association between NAFLD and thyroid dysfunction. Importantly thyroid hormones interact on hepatic lipid homeostasis through multiple pathways including stimulation of free fatty acid delivery to the liver for re-esterification of triglycerides, and increasing fatty acid Beta-oxidation thereby affecting hepatic fat accumulation. Early identification of at-risk patients is important since treatment of the hypothyroidism may reduce the risk of NAFLD and its potential complications.[16]

AIMS AND OBJECTIVES

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To study the relationship between Hypothyroidism and Non-Alcoholic Fatty Liver Disease.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HYPOTHYROIDISM

Thyroid gland is one of the larger endocrine gland in human body. It has two primary functions. The first one is to secrete thyroid hormones by which it maintain the normal level of metabolism in the tissues. Most of the cells in the body consumes O2 in the presence of thyroid hormones and thyroid hormone also help to regulate lipid and carbohydrate metabolism thereby influence body mass and mentation.

The second function of thyroid gland is secretion of calcitonin, a hormone that involved in maintaining the circulating levels of calcium.

Anatomy

Thyroid gland is butterfly shaped that straddles the trachea in the front aspect of neck. The gland weight is about 15 to 20g in adult. It develops from thyroglossal duct; thyroglossal duct extends from the foramen caecum which is present between the middle and posterior third of tongue in the midline. Two lobes of thyroid gland connected by isthmus. Sometimes a pyramidal lobe arising from the isthmus in front of larynx. The gland had richest blood supply. The right lobe is more vascular than the left lobe. Superior thyroid artery is a branch of external carotid artery and inferior thyroid artery is a branch of first part of

subclavian artery. Both of them supplies thyroid gland. Thyroid blood flow ranges from 4 to 6 ml / minute per gram which is more than that of blood flow to the kidneys (3ml / minute per gram). The gland is composed of spherical units called as follicles. Which are invested with rich capillary network. The interior of follicle is filled with colloid. Follicles are lined by follicular cells which are columnar when the gland is active and cuboidal when the gland is inactive.

The thyroid gland also contain para follicular cells or C cells, which secrete calcitonin.

Chemistry and Synthesis of Thyroid hormones:

T3 & T4 are iodine containing derivatives both are derived from thyronine which is a condensation product of two molecule of tyrosine amino acid.

T3 (3,5,3’ triiodothyronine)

T4 (3,5,3’,5’ tetraiodothyronine)

T3 and T4 are stored in the thyroid follicle as a part of thyroglobulin molecule.

1. Iodide uptake

By active transport with the help of $Na^+ I^-$ symporter or NIS channel iodide trapped into follicular cell. This iodide trapping is stimulated by TSH. Iodide content of thyroid gland regulate the uptake

mechanism. Scanty store activating and large store inhibiting the uptake of iodide.

2. Oxidation and Iodination:

Trapped iodide carried across the follicular cells apical membrane with the help of Pendrin transporter. Membrane bound Thyroid peroxidase enzyme convert the iodide into iodinium Ions (I+) or hypoiodous acid (HOI) or Enzyme linked hypoiodate (EOI) with the help of H_2O_2. These forms of Iodine combine with the tyrosil residues of thyroglobulin to form mono-iodo tyrosin (MIT) and di-iodotyrosine (DIT) without any enzymes.

3. Coupling:

T3 & T4 are formed by coupling of iodinated tyrosil residues with the help of TPO. Normally more T4 formed than T3.

4. Storage and release:

Iodinated tyrosil and thyronil residues attached to the thyroglobulin molecules stored as thyroid colloid. When needed the thyroglobulin with its attachment taken up by the thyroid follicular cells by endocytosis and broken down by lysosomes proteases. Released T3 & T4 secreted into the circulation, MIT & DIT residues deiodinated and released iodide is reutilized for iodination.

5. Peripheral conversion of T4 into T3

T4 converted to T3 in the peripheral tissue especially liver and kidney. About 1/3rd of secreted T4 undergoes peripheral conversion, most of the T3 derived from liver.

Target tissues take up T3 for their metabolic requirement, but brain and pituitary take up T4 and convert it into T3 by their own cells.

Oxidation of iodide, coupling, endocytosis and proteolysis of thyroglobulin residues is stimulated by TSH.

Transport and metabolism of thyroid hormone:

Thyroid hormone avidly binds to plasma protein. Most of the protein bound iodine (PBI) in plasma is thyroid hormone. Among this 90-95% is T4 & rest is T3.

Thyroid hormone binds with 3 type of plasma proteins, order of affinity for T4.

(i) Thyroxine binding globulin (TBG)

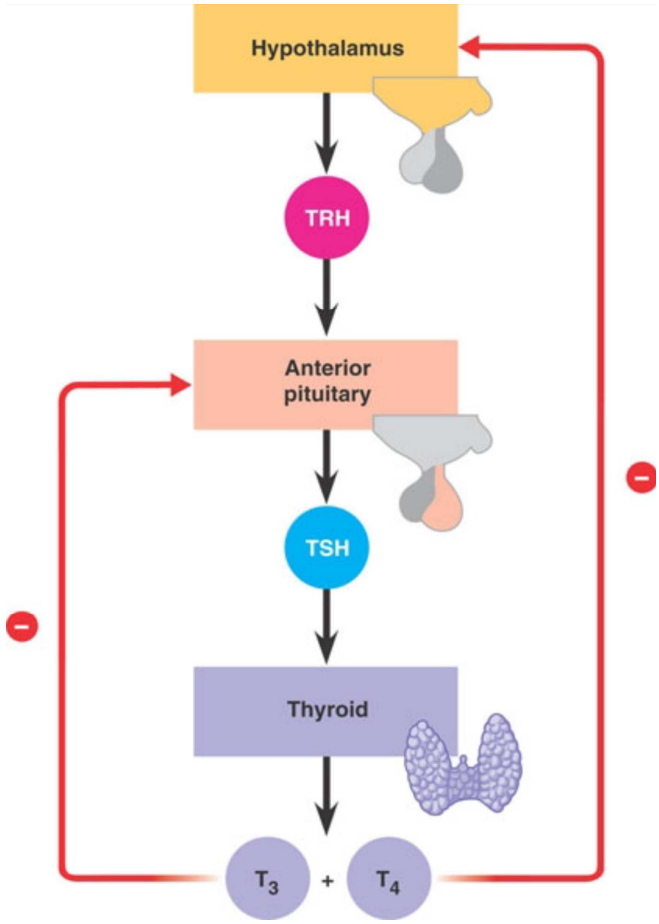
(ii) Thyroxine binding prealbumin also called transthyretin

(iii) Albumin

During pregnancy thyroid binding globulin level is increased so protein bound iodine levels are elevated but free hormones level remain unaltered hence there is no change in the thyroid status.

Metabolic inactivation of thyroid hormones occurs by deiodination and sulfate / glucuronide conjugation of hormones. Primary site of metabolism is liver, salivary gland and kidney also takes part in the metabolism of T3 & T4. The conjugates are excreted in bile. A significant fraction of the hormone enter the enterohepatic circulation after deconjugation finally excreted in urine.

Regulation of Thyroid Hormone



Metabolic function of Thyroid Hormone

Carbohydrate:

Thyroid hormone increases the carbohydrate metabolism. Utilization of sugar by tissues is increased (mainly secondary to increased BMR) . It increases the glycogenolysis and gluconeogenesis in liver and increases the absorption of glucose from intestine.

Lipid:

Lipolysis is indirectly enhanced by T4 and T3 by potentiating the action of catecholamine and other lipolytic hormones. It lowers the circulating cholesterol level before the metabolic rate rises, the plasma cholesterol level drops which indicates that this cholesterol lowering action independent of the stimulation of O2 consumption. The decrease in plasma cholesterol level is due to increased formation of LDL receptors in the liver resulting in increased hepatic uptake of cholesterol from the circulation.

Protein:

Apart from synthesis at certain protein overall effect of T3 is catabolic, most of the protein being used as energy source. Prolonged action of T3 & T4 resulting in negative nitrogen balance and tissue wasting.

Hypothyroidism:

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone. Worldwide iodine deficiency is the most common cause of hypothyroidism.

Epidemiology

Worldwide Iodine deficiency is the most common cause of Hypothyroidism. Autoimmune disease like Hashimoto's thyroiditis and iatrogenic cause like treatment of hyperthyroidism are most common in areas of Iodine deficiency.

World Health Organization (WHO) data from 130 countries taken from January 1994 through December 2006 found inadequate iodine nutrition in 30.6% of the population. The WHO recommends urinary iodine concentrations between 100 and 199 microgram/L in the general population and a range of 150-249 microgram/L in pregnant women. In developed countries, death caused by hypothyroidism is uncommon.

Age related demographics:

The frequency of hypothyroidism, goiters and thyroid modules increase with age. Hypothyroidism is most prevalent in elderly populations with 2-20% of older age groups having some form of hypothyroidism. The Framingham study found hypothyroidism (TSH >10mIU/L) in 5.9% of women and 2.4% of men older than 60 years. In NHANES (The National Health and Nutrition Examination Survey)

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1999-2002 the odds of having hypothyroidism were 5 times greater in persons aged 80 years and older than in individuals aged 12-49 years.

Sex related demographics:

Community studies use slightly different criteria for determining hypothyroidism, therefore female to male ratios vary. Generally, thyroid disease is much more common in females than in males, with reported prevalences ranging from 2 to 8 times higher in females.

Race related demographics:

NHANES 1999-2002 reported that the prevalence of hypothyroidism (including subclinical hypothyroidism) was higher in whites around 5.1% and Mexican Americans than in African Americans 1.7%, African Americans tend to have lower median TSH values.

Causes

Causes of Hypothyroidism
Primary Hypothyroidism
Acquired Hashimoto's thyroiditis Iodine deficiency (endemic goiter) Drugs blocking synthesis or release of T_4 (e.g., lithium, ethionamide, sulfonamides, iodide) Goitrogens in foodstuffs or as endemic substances or pollutants Cytokines (interferon-γ, interleukin-2) Thyroid infiltration (amyloidosis, hemochromatosis, sarcoidosis, Riedel's struma, cystinosis, scleroderma) Postablative thyroiditis due to ^{131}I surgery or therapeutic irradiation for nonthyroidal malignancy
Congenital Iodide transport or utilization defect (NIS or pendrin mutations) Iodotyrosine dehalogenase deficiency Organification disorders (TPO deficiency or dysfunction) Defects in thyroglobulin synthesis or processing Thyroid agenesis or dysplasia TSH receptor defects Thyroidal G_s protein abnormalities (pseudohypoparathyroidism type 1a) Idiopathic TSH unresponsiveness
Transient (Post-Thyroiditis) Hypothyroidism
Following subacute, painless, or postpartum thyroiditis
Consumptive Hypothyroidism
Rapid destruction of thyroid hormone due to D3 expression in large hemangiomas or hemangioendotheliomas
Defects of Thyroxine-to-Triiodothyronine Conversion
Selenocysteine insertion sequence–binding protein 2 (SBP2) defect
Drug-Induced Thyroid Destruction
Tyrosine kinase inhibitor (e.g., sunitinib)
Central Hypothyroidism
Acquired Pituitary origin (secondary) Hypothalamic disorders (tertiary) Bexarotene (retinoid X receptor agonist) Dopamine and/or severe illness
Congenital TSH deficiency or structural abnormality TSH receptor defect
Resistance to Thyroid Hormone
Generalized "Pituitary" dominant

Clinical manifestation

Hypothyroidism commonly manifests as a slowing in physical activity and mentation but may be asymptomatic. Some of the patient present with obstructive sleep apnea secondary to macroglossia or carpal tunnel syndrome. Women can present with galactorrhea and menstrual disturbances. The diagnosis of hypothyroidism mainly based on clinical suspicion and confirmed by laboratory investigation.

Symptoms of Hypothyroidism:

1. Fatigue, loss of energy and lethargy
2. Weight gain
3. Decreased appetite
4. Cold intolerance
5. Dry skin
6. Hair loss
7. Sleepiness
8. Muscle pain, joint pain, weakness in the extremities
9. Depression
10. Mental impairment, emotional liability
11. Inability to concentrate, impaired memory
12. Constipation
13. Menstrual disturbances, impaired fertility
14. Decreased sweating

15. Nerve entrapment syndrome and paraesthesia
16. Blurring of vision
17. Impairment in hearing
18. Hoarseness of voice, fullness in the throat

The following are symptoms specific for hashimoto thyroiditis

1. Feeling of fullness in the throat
2. Painless thyroid enlargement
3. Exhaustion
4. Sore throat, transient neck pain or both

Physical signs of Hypothyroidism

1. Slowed speech and movement
2. Increased weight
3. Pallor
4. Jaundice
5. Coarse, brittle, straw-like hair
6. Coarse facial features
7. Dull facial expression
8. Macroglossia
9. Periorbital puffiness
10. Goitre (simple or nodular)

11. Increased diastolic pressure and decreased systolic pressure
12. Pericardial effusion
13. Bradycardia
14. Abdominal distention
15. Nonpitting edema
16. Hypothermia
17. Hyporeflexia with delayed relaxation, ataxia or both

Severe form of hypothyroidism is myxedema coma. It occur in individually with undiagnosed and untreated hypothyroidism when exposed to an stress like

1. After sedation
2. Pneumonia
3. CCF
4. MI
5. GI bleeding
6. CVA
7. Sepsis
8. Exposure to cold

Feature of myxedema coma are as follows:

1. Altered sensorium
2. Bradycardia
3. Hypothermia
4. Hypercarbia
5. Hyponatremia
6. Cardiomegaly, pericardial effusion, cardiogenic shock and ascites may be present.

Laboratory studies

Third generation – Thyroid stimulating hormone assays is the most sensitive screening tool for primary hypothyroidism.

If TSH levels above reference range we have to measure free thyroxine (FT4) Total T4 is highly protein bound (99.97%) which approximately 85% bound to TBG (Thyroid binding Globulin), 10% bound to transthyretin and remainder bound loosely to albumin.

Binding protein levels can vary by hormonal status, inheritance and in some disease states. Hence Free T4 assays becoming popular. Patient with elevated TSH level (usually 4.5 – 10.0mIU/L) but normal free hormone level considered to have mild or subclinical hypothyroidism.

Anti-thyroid peroxidase (anti TPO) and Anti Thyroglobulin (anti Tg) antibodies used in determining the etiology of Hypothyroidism or in predicting future hypothyroidism. Anti TPO antibodies associated with

increased risk of infertility & miscarriage. Treatment with levothyroxine may lower this risk. In non thyroid illness like gastro intestinal disease, pulmonary diseases, myocardial infarction, sepsis, burns, bone marrow transplantation TSH is normal or decreased, Total T4 normal or decreased and Total T3 levels are markedly decreased this may be confused with secondary hypothyroidism. It is mainly due to decreased peripheral production of T3 from T4. In some critically ill patient TBG levels are decreased in association with abnormality in the hypothalamic pituitary axis. During recovery some patient have transient elevations in serum TSH concentration. Hence TFT is not needed unless thyroid dysfunction strongly suspected and if evaluation warranted. TRH stimulation test is an older test and rarely needed for to assess pituitary and hypothalamic dysfunction with the improvement in TSH and free T4 assays, TRH stimulation become outmoded.

Complete blood count and metabolic profile may be abnormal in patient with hypothyroidism. These abnormalities include anemia, dilutional hyponatremia, reversible increase in serum creatinine, hyperlipidemia. Elevation in creatinine kinase & transaminases. In primary hypothyroidism causes elevation in TRH, which inturn cause elevation of prolactin along with TSH. But prolactin level in patients with hypothyroidism are lower than that of prolactinomas (the latter are usually 150-200ng/ml or higher)

Imaging Studies:

- Ultrasonography of neck and thyroid to detect nodules and infiltrative disorder.
- Hashimoto thyroiditis is mostly associated with diffusely heterogenous ultrasonographic image. In rare case hashimoto thyroiditis may be associated with lymphoma of thyroid. Serial images with FNAC (Fine Needle Aspiration Cytology) of doubtful nodules may be useful.
- Radioactive iodine uptake (RAIU) and Thyroid scanning are not useful in hypothyroidism. Because some level of endogenous thyroid function is necessary for this test. In hashimoto thyroiditis relatively high early uptake (after 4 hrs) but do not have the usual doubling of uptake of 24 hrs consistent with an organification defect.
- Some patient going for F18 fluorodeoxyglucose positron emission tomography for non thyroid disease show significant thyroid uptake as an incidental finding. Diffuse uptake by the thyroid on FDG PET is considered as benign and is typical of thyroiditis.

FNAC

Thyroid nodule found in patients who are in hypothyroid, euthyroid or hyperthyroid state needs FNAC for evaluating the suspicious nodules. Risk factor for thyroid nodule include age more than 60 years, previous history of head or neck irradiation, and a family history suggestive of thyroid cancer.

Approximately 5-15% of solitary nodules are malignant.

TFT Interpretation

1. Euthyroid
    - TSH & Free thyroxine are in normal range.
2. Primary hypothyroidism
    - TSH increased and free thyroxine decreased
3. Secondary hypothyroidism
    - TSH decreased and free thyroxine decreased
4. Subclinical hypothyroidism
    - TSH increased and free thyroxine normal
5. Primary hyperthyroidism
    - TSH decreased free thyroxine increased
6. Secondary hyperthyroidism
    - TSH increased free thyroxine increased
7. Subclinical hyperthyroidism
    - TSH decreased free thyroxine normal
8. Patient on Eltroxin
    - TSH normal, free thyroxine increased

Screening Recommendation

- According to American College of Physicians screening is needed in all women older than 50 years of who or more clinical feature of disease.
- The American Academy of family physicians recommends screening is needed in asymptomatic patients older than 60 years.
- The American Association of clinical endocrinologist recommends TSH measurements in all women with child bearing age before pregnancy or during the first trimester of pregnancy.
- The US Preventing Task Force concludes that the evidence are insufficient to recommend for or against routine screening for thyroid disease in adults.

TREATMENT

Clinical Hypothyroidism:

If there is no residual thyroid function, the replacement dose of levothyroxine is usually 1.6 microgram/kg bodyweight if the daily requirement (typically 100-150 microgram) it should be taken at least 30 min before breakfast. In many patients especially after the treatment of graves disease lower doses suffice until residual thyroid tissue is destroyed (the dose usually 75-125 microgram/d).

Adult less than 60 years of age without any evidence of heart disease may be started on 50-100ug levothyroxine daily. On the basis of TSH level the dose has to be adjusted. The goal of the treatment is to bring the normal TSH ideally in the lower half of the reference range. TSH responses are gradual after levothyroxine replacement. So TFT has to be done after 2 month initiation of treatment. After levothyroxine replacement clinical effects are slow to appear. Patients may not have full relief from symptoms until 3-6 months after normalization of TSH levels. Adjustment of levothyroxine dosage from 12.5microgram or 25 microgram increment if the TSH is high, decrement in the same magnitude if the TSH is low. T4 overtreatment patient can present with suppressed TSH. Symptoms and signs of overtreatment as follows:

1. Tachycardia
2. Palpitation
3. Nervousness
4. Atrial fibrillation
5. Headache
6. Tiredness
7. Increased excitability
8. Sleeplessness
9. Possible angina

When normal body weight patient taking >200 microgram of levothyroxine per day with elevated TSH is a sign of poor adherence to therapy. Some patient have normal or high free T4 level despite elevated TSH because they remember to take medication few days before TFT, this is enough to normalize T4 but not TSH levels.

Conditions That Alter Levothyroxine Requirements
Increased Levothyroxine Requirements
Pregnancy
Gastrointestinal Disorders Mucosal diseases of the small bowel (e.g., sprue) After jejunoileal bypass and small-bowel resection Impaired gastric acid secretion (e.g., atrophic gastritis) Diabetic diarrhea
Drugs That Interfere with Levothyroxine Absorption Cholestyramine Sucralfate Aluminum hydroxide Calcium carbonate Ferrous sulfate
Drugs That Increase the Cytochrome P450 Enzyme (CYP3A4) Activity Rifampin Carbamazepine Estrogen Phenytoin Sertraline
Drugs That Block T_4-to-T_3 Conversion Amiodarone
Conditions That May Block Deiodinase Synthesis Selenium deficiency Cirrhosis
Decreased Levothyroxine Requirements
Aging (≥65 yr) Androgen therapy in women

T_4, Thyroxine; T_3, triiodothyronine.

Subclinical Hypothyroidism:

Subclinical hypothyroidism defined as biochemical evidence of thyroid hormone deficiency in patients who have few or no apparent clinical feature of hypothyroidism.

Indication of levothyroxine in subclinical hypothyroidism

i) Women who plan to conceive or is pregnant
ii) TSH levels >10mIU/L
iii) TSH levels <10mIU/L with symptoms of hypothyroidism, positive TPO antibodies or evidence of heart disease.

It is important to confirm that elevation of TFT is more than 3 months periods before starting levothyroxine therapy. Treatment is starting with low dose of levothyroxine (25-50 microgram/d) with the aim of normalizing TSH.

The TFT has to be checked annually if levothyroxine is not given.

Special Treatment Considerations:

It is important to ensure that the women who are hypothyroid become euthyroid before conception since maternal hypothyroidism adversely affect fetal neural development and lead to preterm delivery. Presence of thyroid autoantibodies in a euthyroid patient can cause miscarriage and preterm delivery. Thyroid function should be checked immediately after pregnancy confirmed and it should be monitored every

4 weeks during the first half of pregnancy and every 6-8 weeks depending on the levothyroxine dose adjustment is ongoing in the next half of pregnancy usually after 20^{th} weeks of gestation. Upto 50% increase in the levothyroxine dose is needed during pregnancy. The goal of TSH is less than 2.5 mIU/L in the first trimester, less than 3.5 mIU/L during the second and third trimester. Thyroxine level returns to pre pregnancy level after delivery. Pregnant women should be counseled that levothyroxine has to be taken at an interval of atleast 4 hour when she is taking vitamins & iron supplements.

Elderly patient require 20% less thyroxine dose when compared with adults.

Elderly patient associated with coronary artery disease the starting dose of levothyroxine is 12.5-25 microgram/d every 2-3 months the dose has to be adjusted in the similar increment until the TSH is normalized.

Elective surgery in a hypothyroid patient should be deferred until patient achieved euthyroid state. But in untreated hypothyroid patient the emergency surgery is generally safe.

Myxedema Coma

Single IV bolus of levothyroxine 500 microgram as a loading dose is given followed by levothyroxine 50-100 microgram/day at the first instance of clinical suspicion of Myxedema coma. If IV preparation is not available, the same initial dose can be given via Nasogastric tube (but

absorption may be impaired in myxedema). An alternative is liothyronine (T3) in the dose of 10-25 microgram every 8-12hr IV (or) via NG tube because peripheral conversion of T4 to T3 is impaired in myxedema coma. Another option is combination of levothyroxine 200 mcg & liothyronine 25 mcg in a single initial IV bolus followed by levothyroxine 50-100 mcg/day and liothyronine 10 mcg every 8 hr. Parenteral hydrocortisone at a dose of 50mg every 6^{th} hourly is given to combat impaired adrenal reserve associated with profound hypothyroidism. Supportive therapies are given

1. External warming is indicated when the body temperature is $<30^0$ C because it can cause cardiovascular collapse. Space blanket should be used to prevent further heat loss.
2. Broad spectrum antibiotics pending the exclusion of infections.
3. Ventilatory support with regular ABG in the first 48 hour.
4. Hypertonic saline for hyponatremia
5. IV glucose for hypoglycemia

NON-ALCOHOLIC FATTY LIVER DISEASE

Introduction

Nonalcoholic fatty liver disease is the most common cause of chronic liver disease. In hepatic steatosis, the accumulated fat is mostly triglyceride, cholesterol and phospholipids in excess 5-10% of whole liver weight. Histologically, NAFLD can be divided into non NASH fatty liver and NASH (Non Alcoholic SteatoHepatitis). NASH can progress to cirrhosis. So NAFLD encompasses a spectrum of liver pathology with different types of clinical prognoses.

NASH is a common cause of cryptogenic cirrhosis, which account for 10-20% of all cirrhosis.

The definition of non alcoholic fatty liver disease requires that there is evidence of hepatic steatosis either by imaging or by histology and there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, hereditary disorders or steatogenic medication.

In most of the patient, NAFLD is associated with metabolic risk factors such as diabetes mellitus, obesity and dyslipidemia. NAFL is defined as the presence of hepatic steatosis without evidence of hepatocellular injury in the form of ballooning of hepatocyte. NASH is

defined as the presence of hepatic steatosis and inflammation associated with hepatocyte injury (ballooning) with or without fibrosis.

Incidence and prevalence in the general population:

Limited number of studies only investigated about the incidence of NAFLD. Two Japanese studies reported an incidence rate of 31 and 86 cases of suspected NAFLD per 1000 person – years respectively where as another study from England showed a much lower incidence rate of 29 cases per 100000 person – years and more studies are needed to understand better about the incidence of NAFLD across different age, geographic and ethinic groups.

The reported prevalence of NAFLD varies widely depending on the population studied and definition used. The prevalence of histologically defined NAFLD was 20% and 51% in two different studies comprised of potential living liver donors.[12,13] The reported prevalence of NAFLD when defined by liver ultrasound ranged between 17% and 46% depending on the population which studied.[17] In study consisting of nearly 400 middle aged individuals, the prevalence of NAFLD defined by ultrasonography was 46% and the prevalence of histologically confirmed NASH was 12.2%,[14] in the Dallas Heart study, when assessed by MR spectroscopy the prevalence of NAFLD in general population was 31%.[15] The prevalence of suspected NAFLD when estimated using amino

transferases alone without imaging or histology ranged between 7% and 11% but aminotransferases can be normal in individuals with NAFLD.[17] In summary, estimates of the worldwide prevalence of NAFLD ranges from 6.3% to 33% with a median of 20% in the general population based on the variety of assessment methods.[17] On the other hand the estimated prevalence of NASH is lower ranging from 3 to 5%.[17] The prevalence of NASH with cirrhosis in the general population is not known.

Prevalence of NAFLD in High risk groups

Obesity is a common and well documented modifiable risk factor for NAFLD. Both excessive BMI and visceral obesity are the risk factors for NAFLD. In patient with severe obesity undergoing bariatric surgery, the prevalence of NAFLD can exceed 90% and upto 5% of patient may have in suspected cirrhosis. There is a very high prevalence of NAFLD in individuals with type 2 diabetes mellitus (T2DM).[17]An ultrasonographic study of patient with T2DM showed on 69% prevalence of NAFLD. In another study 127 of 204 diabetic patients delayed fatty infiltration who consented to biopsy had histologic confirmation of NAFLD. High serum triglyceride levels and low serum HDL levels are very common in patient with NAFLD. The prevalence of NAFLD is individually with dyslipidemia who are all attending lipid clinics was estimated to be 50%.

Age, gender and ethnicity are also associated with a differential prevalence for NAFLD.[17]A number of studies have shown that the prevalence of NAFLD increases with age. The likelihood of disease progression to advanced fibrosis or mortality increases in older patients with NAFLD. Many recent studies have reported that male gender is a risk factor for fatty liver disease.[17] For example, in a study of 26527 subjects undergoing medical checkups, the prevalence of NAFLD way 16% in women but 31% in men.[18] Compared to non hispanic whites, hispanic individuals have significantly higher and non hispanic blacks have significantly lower prevalence of NAFLD.[19]

The prevalence of NAFLD in American – Indian and Alaskan – Native populations appears lower, ranging from 0.6% to 22%, although the lack of histologic definition makes it likely that is an underestimate.[20]

RISK FACTORS ASSOCIATED WITH NAFLD

(i) Condition with established association:
1. Obesity 2. T2 DM 3. Dyslipedimia 4. Metabolic syndrome
(ii) Condition with emerging association
1. Polycystic ovary syndrome 2. Hypothyroidism 3. Obstructive sleep apnea 4. Hypogonadism 5. Hypopituitarism 6. Pancreato – duodenal resection

The adult treatment panel III definition of metabolic syndrome requires the presence of 3 or more of the following

1. Waist circumference

   >102 cm in men or

   >88 cm in women

2. Triglyceride level 150mg/dl or greater

3. High density lipoprotein (HDL) cholesterol level less than 40mg/dl in men are less than 50mg/dl in women.

4. Systolic BP 130mmHg or greater (or) diastolic BP 85mmHg or greater

5. Fasting plasma glucose level 110mg/dl or greater

Alcohol consumption and definition of NAFLD

NAFLD indicates the lack of any evidence of ongoing, or recent consumption of significant quantities of alcohol. However the precise definition of significant alcohol consumption in patient with NAFLD is uncertain.

A recent consensus meeting[21] concluded that for NASH clinical trials, significant alcohol consumption be defined as >21 drinks per week in men and >14 drinks per week in women over a 2 year period prior to baseline histology. The definition of significant alcohol consumption in the published NAFLD literature has been inconsistent and ranged from >1 alcoholic drink (~ 10 grams of alcohol per one drink unit) per day to >40 grams per day and published studies have not be used gender – specific definitions.[22]

In general daily consumption of less than 20g in women and 30g in men resulting in a low risk for the development of alcoholic liver injury. Life time ethanol exposure rather than daily consumption suggest that about 10% of patient with NASH may have a component of alcohol related steatohepatitis.

Causes of fatty liver diseases

Acquired Metabolic disorder:

1. Diabetes Mellitus
2. Obesity
3. Dyslipidemia
4. Kwashiorkor and Marasmus
5. Rapid weight loss
6. Starvation

Cytotoxic and cytostatic drugs

1. L-asparaginase
2. Azacitidine
3. Cisplatin
4. Bleomycin
5. Methotrexate
6. 5-Flurouracil
7. Tetracyclines (inhibit mitochondrial beta oxidation)

Other Drugs and Toxins

1. Amiodarone
2. Camphor
3. Chloroform
4. Ethanol

5. Cocaine
6. Ethylbromide
7. Glucocorticoids
8. Estrogens
9. Griseofulvin
10. Lycopodium serratum
11. HAART (Zidovudine, Stavudine, Didanosine)
12. Nitrofurantoin
13. Nifedipine
14. Tamoxifen
15. NSAIDS (Piroxicam, ibuprofen, Indomethacin, sulindac)
16. Valproic acid

Metals:

1. Barium salts
2. Antimony
3. Mercury
4. Chromates
5. Phosphorus
6. Thallium components
7. Rare earth metals at low atomic number
8. Uranium components

Inborn Errors of Metabolism

1. Abetalipoproteinemia
2. Galactosemia
3. Familial hepatosteatosis
4. Heriditary fructose intolerance
5. Glycogen storage disease
6. Systemic carnitine deficiency
7. Homocystinuria
8. Tyrosinemia
9. Wilson disease
10. Weber Christian Syndrome

Surgical Procedure

1. Biliopancreatic diversion
2. Extensive small bowel resection
3. Jejunoileal bypass

Miscellaneous condition

1. Industrial exposure to petrochemicals
2. IBD
3. TPN
4. Jejunal diverticulosis with bacterial overgrowth
5. Partial lipodystrophy

Pathogenesis of NAFLD

Hepatocellular injury in NASH can be explained by TWO hit hypothesis accumulation of fat in the hepatocytes followed by oxidative injury.

Mechanism of Steatosis

Imbalance between the overall calorie intake and systemic calorie utilization results in lipid accumulation in the liver. Hepatic fat results from synthesis of new fatty acids from carbohydrate precursors by de novo lipogenesis, uptake of circulating non-esterified fatty acids (NEFA) derived from lipolysis of adipose tissue. Uptake of diet derived chylomicron remnant or uptake of very low density lipoprotein (VLDL) derived low density lipoprotein (LDL) remnants. Hepatic fat can be disposed of by either lipoprotein secretion especially as VLDL or oxidation. NAFLD appears to be developed especially by NEFA uptake, altered lipid export and de novo lipogenesis.

Regulation of lipid synthesis:

In the hepatocytes, lipid stores are mainly regulated by two transcription factors namely sterol regulatory element binding protein (SREBP) which governed by insulin and dietary fatty acids and carbohydrate response element binding protein (CREBP) which inturn

governed by ambient glucose levels.[23,24,25] CREBP and SREBP stimulate nuclear transcription of the various enzymes responsible for fatty acid synthesis and subsequently their esterification into triglycerides, they stored as triacylglyceride within cytosolic fat droplets or exported as VLDL.

Biochemistry of de novo lipogenesis:

De novo lipogenesis of fatty acid starts from translocation of carbohydrate derived acetyl CoA subunits as citrate which passes through the mitochondrial membrane to the cytosol. ATP dependent cytosolic condensation of acetyl subunits into palmitic acid depends on the activity of a key enzyme molecule acetyl CoA carboxylase, which is regulated by adrenaline (epinephrine). Insulin and glucagon and which converts the acetyl CoA into malonyl CoA. Then malonyl CoA goes for series of condensation reaction catalyzed by fatty acid synthase forms palmitic acid. Malonyl CoA by blocking the carnitine shuttle (In which fatty acids destined for oxidation are moved into the mitochondrion) inhibits mitochondrial Beta oxidation of fatty acids.

After formation of palmitic acid which can undergo elongation in the endoplasmic reticulum to long chain and very long chain fatty acids. Palmitate combine with glycerol after desaturation to form mono-, di- and triacylglycerol (triglycerides). They are incorporated into the fat droplets

in the endoplasmic reticulum or packaged by the activity of microsomal triglyceride transfer protein in association with apolipoprotein B100 (apoB100) for secretion of VLDL.[26]

Steatosis in humans

Based on the studies by using radio labeled precursors, in triglycerides synthesis 59% from uptake of adipose – derived NEFA, 26% by denovolipogenesis (driven by SREBP and CREBP) and 15% by dietary sources.[27] The NEFA derived from the visceral adipose tissue due to failure of insulin to suppress the hormone sensitive lipase at adipose stores. The incorporation NEFA into triglycerides and their contribution in steatosis mainly depends on acyl CoA: diacylglycerol acyl transferase 1 (Dgat1).[28]The secretion of apoB100 of normal VLDL is impaired in NAFLD and correlate with the secretion of a larger VLDL particle with greater triglyceride content relative to it apoB100.

Mitochondrial dysfunction:

Energy deficient state evidenced as diminished ATP content associated with accumulation of lipids in the liver. The mitochondria appears to be both a target and a source of pro-oxidant free radicals (superoxide and hydroxyl radicals) the effects of which present in NASH, absent in NNFL, Mitochondrial swelling and intra mitochondrial crystals.

Impaired function of mitochondrial electron transport chain is due to over expression of uncoupling protein and to dysfunction of components of the electron transport chain.[29]Around 40-70% of activity reduced in all of the major complexes (I-V) of Electron transport chain in human NASH[30]. Increased mitochondrial permeability leading to release of mitochondrial cytochrome and apoptosis signaling. Increased mitochondrial cholesterol related with mitochondrial dysfunction and increased mitochondrial permeability.[31]

Lipid composition in Non-alcoholic fatty liver

Recent lipidomic analysis of liver tissue in NAFLD have shown significant differences in NNFL versus NASH stepwise increases of triacylglycerol : diacylglycerol and free cholesterol : phosphotidylcholine ratios were noted from normal to NNFL to NASH. Eicosapentanoic acid and docosahexanoic acid are polyunsaturated fatty acid which were relatively lower in NASH leading to an elevated N6:N3 ratio, suggesting a relative excess of proinflammatory N6 fatty acids such as arachidonic acid. A potentially toxic intermediary in sphingolipid metabolism is ceramide, increased level of which is in peripheral white adipose tissue detected in obese patients with fatty liver.[32]

Lipid peroxidation in non alcoholic steatohepatitis

Impaired control of aerobic metabolism resulting in oxidative stress and lipid peroxidation leads to cellular injury in lipid loaded

hepatocyte[33]. Although cytochrome P-450 or peroxisomal fatty acid oxidation may contribute the formation of free radical, the superoxide radical is primarily derived from mitochondria. Once superoxide radical formed it is metabolized by superoxide dismutase to hydrogen peroxide. Hydroxyl radical are derived from decay of hydrogen peroxide in the presence of Fe2+ via the Fenton or Haber-weiss reactions. If the hydroxyl radicals are not detoxified by glutathione will damage the cellular constituents like membrane fatty acids, protein and DNA through direct binding[34]. Fatty acids injury produces lipid peroxidation – a branching chain reaction which stimulated by a free radicals attack on unsaturated fatty acids which inturn produces another free radical and lipid hydroperoxide. Lipid hydroperoxide degrades in a reaction catalyzed by iron to form a second lipid based free radical, it will amplify the oxidation pathway.[35] Oxidative injury to the phospholipid membrane of small fat droplets which contain insulin sensitive lipases and the endoplasmic reticulum involved in the development of cellular ballooning, impaired disposal of toxic free fatty acids and hepatic insulin resistance, other by products of oxidative injury include metabolite of nitric oxide particularly in macrophages and neoantigens formation which may be linked to serum IgA level elevation.

Autophagy, Lysosomes, Fatty acid induced injury and apoptosis

Lysosome mediated autophagy involved in disposal of accumulated and presumably injured fat droplets. Impaired formation if triglycerides from diglyceride due to polymorphisms in the enzyme Dgat (or) acyl CoA: diacylglycerolacyltransferase and it also contribute to impaired disposal of free fatty acids[36]. Lysosomal permeability increased by free fatty acids leading to release of cathepsins (crysosomal proteases), which inturn associated with changes in mitochondrial permeability. Cathepsin increases the release of mitochondrial cytochrome C which activates caspases leading to activation apoptotic pathways.

Endoplasmic reticulum stress, activation of inflammation, fibrosis and cell death:

Final cell death in hepatocytes result from combination of necrosis and apoptosis (necroapoptosis). Activated caspase 3 produce fragmentation of cytokeratin 18. This fragmented cytokeratin produces Mallory-Denk bodies which is best seen in the ballooned hepatocytes. Impaired function of endoplasmic reticulum associated APOB100 due to accumulation of free fatty acids and it contribute to ER stress with accumulation of misfolded proteins within the ER.[37] Stressed ER induce proinflammatory cytokines such as interlactin 8, through the activation of transcription factors such as NF-KBeta (Nuclear factor kappa Beta and

JNK [C-Jun N-terminal kinase]. Depending upon the ER stress JNK is activated finally these pathways produces accumulation of inflammatory infiltrates and activation collagen producing hepatic stellate cells characterized by transition form a Vitamin-A rich quiescent cell to myofibroblast.[38] Fibrosis progression depends on the altered repair process with impaired hepatocyte replication and increased hepatic progenitor cells activity leads to a ductular reaction in the portal tracts.

The ballooned cell:

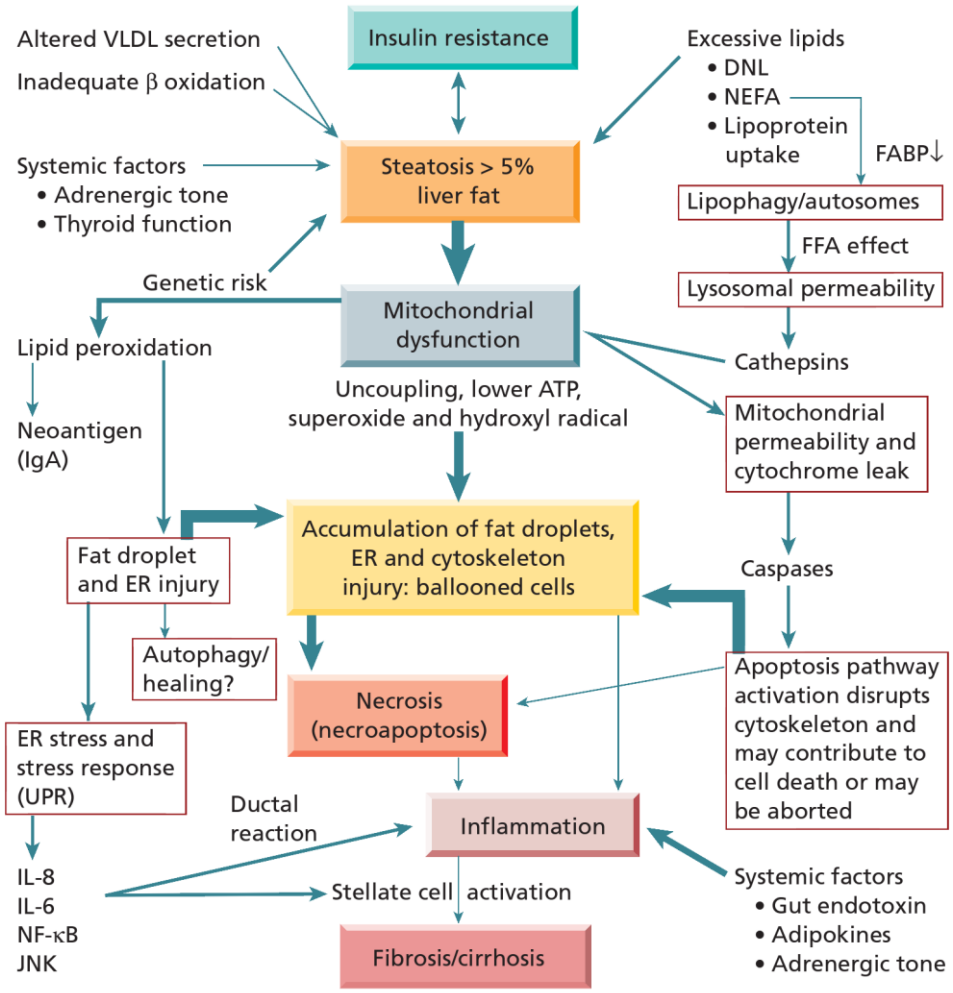
Ballooned hepatocytes are identifiable by deficiency of intact cystokeratin.[39] It is associated with active steatohepatitis. Ballooned cell consists of an accumulation of multiple small fat droplets, distorted mitochondria, dilated ER and Mallory denk bodies. Thus there is simultaneous failure of multiple pathways. So this process can be described as multiorganelle failure. The final event mostly likely is necrosis although apoptotic pathways also play a substantial role and thus can be labelled as necroapoptosis.

Systemic Factor

Insulin resistance commonly associated with NAFLD. It is primarily mediated by excessive free fatty acids and it occurs in multiple

insulin end organs which includes skeletal muscle, adipose tissue and liver. Insulin resistance at molecular level is characterized by shift from tyrosine. Phosphorylation in the insulin receptor substrate to serine phosphorylation which blunts the anabolic effect of insulin.

Pathogenesis



Working classification of NAFLD.

NNFL

Type I NAFLD : Steatosis with no inflammation or fibrosis.

Type 2 NAFLD : Steatosis with nonspecific lobular inflammation but absent of fibrosis or hepatocyte ballooning.

NASH

Type 3 NAFLD : Steatosis with inflammation and fibrosis of variable levels (NASH)

Type 4 NAFLD : Steatosis, inflammation, hepatocyte ballooning and fibrosis (or)Mallory-Denk bodies (NASH).

Histopathologic features of NAFLD

Present in all or most cases:

Macrovesicular steatosis:

- Diffuse or centrilobular steatosis; degree may correlate with BMI

Parenchymal inflammation :

- Polymorphonuclear neutrophils, lymphocytes and other mononuclear cells.
- Hepatocyte ballooning degeneration

Observed with varied frequencies

Perivenular, perisinusoidal or periportal fibrosis (37%-84%) moderate to severe in 15% - 50%. Most prevalent in Zone 3 (perivenular), cirrhosis (7%-16%) in the index biopsy specimen)

- Glycogenated nuclei
- Mallory – Denk bodies
- Stainable hepatic iron
- Lipogranulomas

Clinical features:

Usually patient present with malaise, fatigue, right upper quadrant discomfort, disturbed sleep, chronic pain disorder, achy muscles. Physical examination may reveal enlarged liver, right upper quadrant tenderness, abdominal obesity. Most common presentation of NAFLD is mildly abnormal aminotransferases during routine clinical evaluation. There is also a tendency to decline in the aminotransferases parallel with decreasing steatosis as the fibrosis worsens. And also we have to examine the patient closely for stigmata of cirrhosis including a firm and palpable liver and cutaneous signs such as spider angioma and palmar erythema as well as laboratory signs such as thrombocytopenia. Patient can also present with complications of portal hypertension and occasionally present with acutely decompensated, but previously unrecognized

disease. Gastric central vascular ectasia producing gastrointestinal bleeding sometimes seen. Most patient also have impaired exercise tolerance which is measured by oxygen consumption during graded exercise. This finding is consistent with metabolic obesity even in those patient with low body mass index. The average age for NASH patient presentation is 40-50 years and for NASH related cirrhosis is 50-60 years. Other physical findings in NAFLD is acanthosis nigricans (pigmentation and skin thickening in the posterior neck and axillae) it is more common in children. A prominent dorsal fat pad called as buffalo hump is common and has been associated with more severe histological disease.[40] Some patient also associated with evidence of lipodystrophy.

Laboratory Testing

Serum aspartate amino transferase and alanine amino transferase elevations are usually less than two times of normal.[41]Sometimes in significant disease the amino transferase levels may be within normal limit. Aminotransferase pattern can helpful in staging NASH, as an AST : ALT ratio greater than, suggests progression to more advanced fibrosis[42]. However this pattern is less reliable in patients who are on thiazolidinediones or statin medications.

- Oxidative injury and the formation of Neoantigen with a biliary mucosal B cell response results in elevated serum IgA level.

- Hyperuricaemia results from abnormalities in ATP metabolism leads to accumulation of ADP and excessive purine disposal.
- ANA are detected in 25-30% of NASH patient, the mechanism of their development is not known.
- Hypothyroidism have also been associated with NAFLD.
- There are no consistent patterns of dyslipidemia although hypertriglyceridaemia is commonly found.
- Insulin resistance can be measured by QUICKI test (Quantitative insulin sensitivity check index) or the HOMA test (Homeostasis Model Assessment) both of them are derived from the euglycemic hyperinsulinemic clamp test by the use of mathematical modeling of fasting insulin and glucose levels.
- When the abnormal liver biochemical test or suspected NAFLD imaging studies can be done.
- Hepatic USG may shows bright liver of increased echogenicity consistent with hepatic steatosis in CT fatty liver is lower density than the spleen and in MRI fat appears bright on T1 weighted imaging. A study that assessed the sensitivity of the imaging MRI, Abdominal CT and USG for distinguishing advanced NASH from simple steatosis showed that USG & CT had sensitivity of 100% and 93% respectively for detecting hepatic fat involving greater

than 33% of liver with positive protective values of 62% and 76% respectively. No imaging modality can able to distinguish simple steatosis from more advanced forms of NAFLD. In some traditional cross sectional imaging studies support the diagnosis of NAFLD but cannot predict the severity of disease and cannot replace the liver biopsy for establishing the diagnosis with certainty.

Role of Liver Biopsy

Diagnosis of NAFLD is relatively easy to make when the hepatic steatosis is seen on gross sectional imaging and other chronic liver diseases are excluded, inspite of that a liver biopsy is still required to identify the patients with NASH. But most of the patients with NAFLD do not undergo a liver biopsy. Because liver biopsy is an invasive procedure associated with rare but severe complications which including hemorrhage and even death. The ability to differentiate NASH from NNFL is critical because patients with NASH are at risk of progression to cirrhosis.

Indication for liver biopsy:

- Liver biopsy should be considered in patient with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis.

- The presence of metabolic syndrome and the NAFLD fibrosis score may be used for identifying patient who are at risk for steatohepatitis and advanced fibrosis.
- Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded without a liver biopsy.

Non-Invasive Assessment of Steatohepatitis and Advanced Fibrosis in NAFLD

1. The NAFLD fibrosis Score
2. Enhanced liver fibrosis (ELF) score
3. Transient Elastography
4. Circulating levels of cytokeratin 18 (CK18)

1) NAFLD Fibrosis Score

It takes into account the patients age, body mass index, blood glucose levels, aminotransferase levels, platelet count and albumin.

- The score <-1.455 : predictor of absence of significant fibrosis (Fo-F2 fibrosis) negative predictive value of 88 percent; sensitivity 77 percent, specificity 71 percent.
- Score > -1.455 to < 0.675 indeterminate score.

- >0.675 predictor of presence of significant fibrosis (F3-F4 fibrosis) (Positive predictive value for advanced fibrosis 82 percent; sensitivity 43 percent, specificity 96 percent).
    - FO - No fibrosis
    - F1 - Portal fibrosis without septa
    - F2 - Few septa
    - F3 - Numerous septa without cirrhosis
    - F4 - Cirrhosis

2) Enhanced Liver Fibrosis (ELF) Score:

It is an extracellular matrix marker test consisting of tissue inhibitor of metallo proteinases 1 (TIMP-1), aminoterminal properties of Type III Procollagen (PIII NP) and Hyaluronic acid (HA) showing good correlations with fibrosis stages in chronic liver disease.

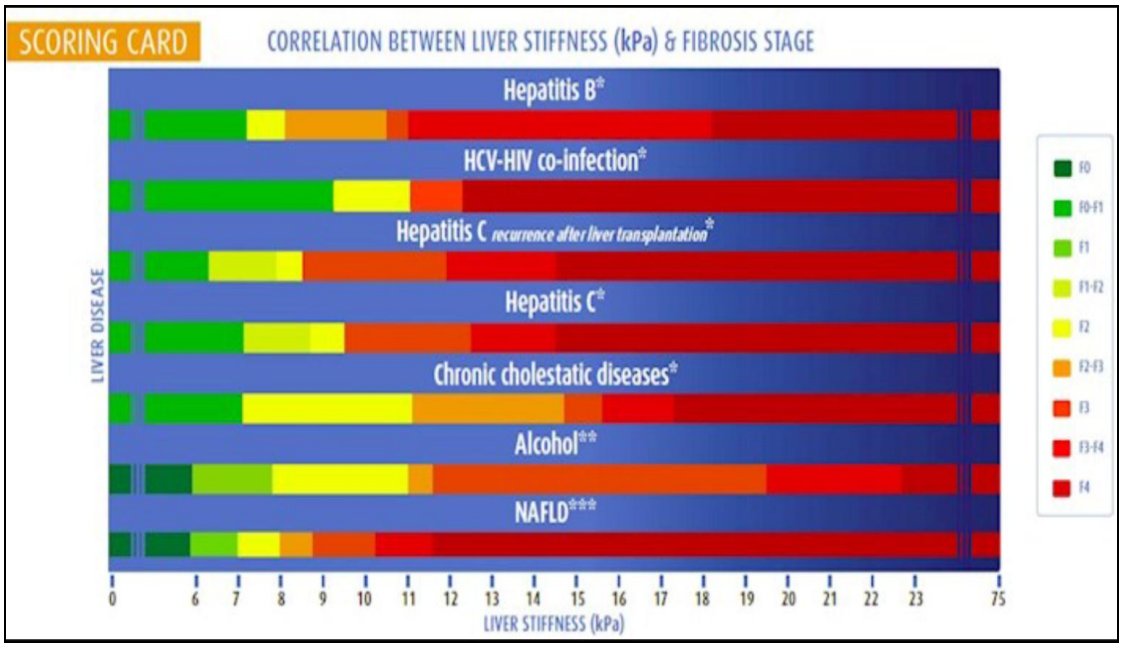
Patient with advanced liver fibrosis having the ELF Score of 10.51 or above.

When the ELF Score below 10.51

- Those patient are unlikely to have advanced fibrosis.
- And reassessment of advanced liver fibrosis every 3 years for adults and every 2 years for children and young people is sufficient for regular monitoring.

3) Transient elastography:

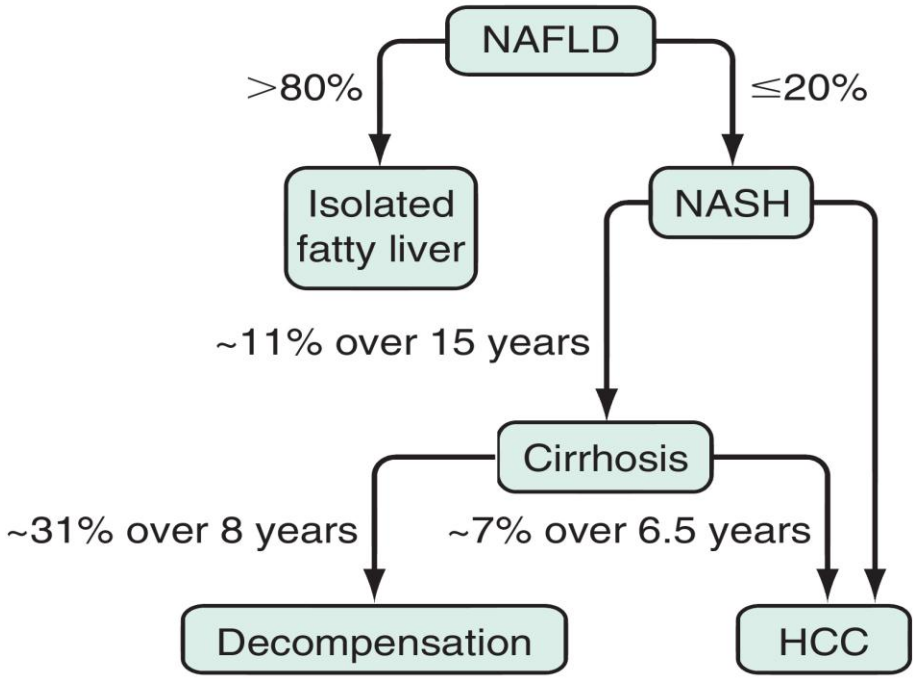
Fibroscan can be done by the method called as transient elastography. In which we uses a low amplitude shear wave that propagates through the liver parenchyma. The liver stiffness is calculated by the speed at which the waves are moving and it measured in kilopascals. Optimal cut off values to predict fibrosis stage have varied among studies. The limitations of this study include decreased accuracy in the setting of obesity, narrow intercostal spaces, hepatic venous congestion, extrahepatic cholestasis and acute inflammation. An XL probe has been developed to increase diagnostic accuracy in obese patients.



Other types of elastography:

1. Acoustic radiation force impulse elastography (ARFI) by this technique the velocity of short duration, high intensity acoustic pushing pulse in the liver. Pilot trials have suggested accuracy similar to that of US elastrography, with an area under operating curve (AUROC) of 0.973 in a trial of 54 Japanese NAFLD patient.[43]
2. MR elastrography (MRE) can be done with the combination of MRI and elastrography. MRE appears to better than transient elastrography in differentiating mild from moderate to severe NAFLD.

Natural history of NAFLD



Nature history of non-alcoholic fatty liver disease including NNFLD & NASH. Isolated fatty liver rarely if ever progress to cirrhosis and it is not associated with an increased risk of death compared within the general population. NASH is associated with increased risk of death due to cardiovascular disease, malignancy and cirrhosis and its complications. Progression of fibrosis in NASH is associated with DM, Severe insulin resistance, weight gain >5kg, higher BMI, rising serum aminotransferases levels and cigarette smoking.[44]

Treatment of NAFLD

The management of patients with NAFLD consists of treating the liver disease as well as the associated metabolic co-morbidities such as hyperlipidemia, obesity, insulin resistance and T2DM. As patients with NAFLD without steatohepatitis have excellent prognosis.

Life style intervention

Many studies indicates that life style modification may reduce aminotransferase levels and improve steatosis when measured either by ultrasound or MR Imaging and spectroscopy. NAFLD can be treated atleast in early stages by conservative approaches such as increased physical conditioning and dietary weight loss. Two controlled trials of dietary weight loss with exercise in both paediatric and adult patients using histologic end points demonstrated improved steatosis,

inflammation and cell injury. Drastic calorie restriction can lead to decreased hepatic fat in as little as 11 weeks but this approach is not sustainable for long term. Most common diet plans appear to be effective in achieving weight loss and the choice of the diet should be individualized according to the patient.[45]

Orlistat has give some benefit in augmenting weight loss but not offer a significant advantage overall.[46]

The amount of weight loss and the frequency intensity of exercise that needed to produce these effects is uncertain, but 10-15% weight reduction cause hepatic fat to dissipate.[47] Waist circumference is used as a surrogate marker for visceral adiposity, more frequent and intense exercise is better. Structured exercise programmes with professional contact give more advantages.[48] Sustained exercise will improve glucose disposal in the mitochondria of skeletal muscle, which is impaired in diabetes. Exercise without weight loss can also alter hepatic histology.[49]This relationship supports the 'fit fat' concept, it is important point to make the patients who may be discouraged if exercise doesn't produce weight reduction[50] some changes in dietary composition can produce relatively little effort. For example elimination of high fructose corn syrup in sweetened beverages may be benefit, because this sweetener can produce equal amount of triglyceride accumulation in the

liver of animals and humans.[51] Supplementation of omega 3 fatty acids in NAFLD is beneficial.[52]

PHARMACOLOGICAL INTERVENTION

Compliance with life style modification is often limited. Pharmacological interventions can be considered in patients with active and potentially progressive disease who fail life style modification. However till to date no specific pharmacological agent has been shown to be beneficial in treating NAFLD. Drugs can be divided into cytoprotective and antioxidants, insulin sensitizer, modulators of fat metabolism and more specific modulators of specific intracellular pathways.

Cytoprotective agents and antioxidants

Ursodeoxycholic acid (UDCA) is a tertiary bile acid, first tested in an early placebo - controlled trial in NASH by using about 15mg/kg, similar improvement in aminotransferases, weight loss and histological parameters were seen in both treated groups, that indicating no benefit.[53] UDCA and Vitamin E supplements compared double placebo or vitamin E and placebo showed steatosis reduction but there is no improvement in other histological parameters in the end of treatment biopsies.[54] Another recent study using higher dose of UDCA did not show clear benefits. UDCA conjugated with Taurine have also undergone preliminary studies.

Betaine (which replenishes glutathione stores and promotes secretion of fat as VLDL), S-adenosylmethionine and combination of Vit E and Vit C are all reported in the pharmacological therapy[55]. A recent controlled trial showed positive results with high dose Vit E (800IU/d) compared with pioglitazone, Vit E improved NASH on biopsy (Vit E Vs Placebo) (43% Vs 19% p=0.001).[56]

Insulin Sensitizers

Pilot studies on metformin have had variable results although there may be a role in children (now in study).[57] But thiazolidinediones produces consistent reduction in steatosis, inflammation and cell injury but if no action on fibrosis[58]. This agent will act on PPAR gamma receptor especially in the adipose tissue, result in shift or fat from the liver to the peripheries, the exact mechanism of this action is not known. Pioglitazone is the most consistently effective agent, although it produce peripheral (adipose) weight gain is a significant problem with all forms of thiazolidinediones.[59]

Lipid Modulations drugs

There is a clear cut association between NASH and hyperlipidaemia, but less is known about the role of fibrates (PPAR alpha agonists favouring fatty acid oxidation) and stains (HMG COA reductase inhibitors) in treating NASH. Several consistent points have emerged from the literature. First in statin treated NASH patients, serum aminotransferases are not reliable indices to assess drug induced benefit or injury. Due to minor fluctuation in the aminotransferases should not lead to stopping of statins. Secondly there may be a subpopulation of patients who have histological improvement, and also another group with increased risk of progression to advanced fibrosis. However a recent controlled trial showed no benefit from 12 months of simvastation.[60]

Other Pharmacological agents:

1. Agents that modulate the angiotension pathway – angiotension receptor blocker such as telmisartan inhibit the hepatic stellate cell activity leading to reduction in the hepatic fibrosis.
2. Agents aimed at the Grehlin – Leptin (satiety) pathway.
3. Antiplatelet agents aimed at blocking profibrotic factors.
4. Agents which modulate ER stress.
5. Adenosine receptor blockers
6. TNF antagonists including pentoxifylline[61]

Bariatric surgery

Bariatric surgery is generally reserved for patients with severe obesity (BMI >40) or presence of comorbidities such as sleep apnoea with BMI>35. In take stage of NASH (Stage 3-4) associated with portal hypertension increases operative risk as does advancing age. So that the use of surgery requires an individual assessment of the risk benefit balance.

Liver Transplantation

The third most common indications for liver transplantation after cirrhosis by HCV and Alcoholic liver disease is NASH cirrhosis. In 2020 it is expected to become the number one indication for liver transplantation.[62] Co-morbid condition limit the eligibility for transplantation and although 30 days mortality following liver transplantation higher in patients with NASH cirrhosis. 1 to 3 year mortality rates are similar to other indications for liver transplantation. Cardiovascular events are increased in patient with NASH cirrhosis undergoing for liver transplantation especially during the perioperative period when compared with patients who are transplanted for alcoholic cirrhosis.[63] 5 years after transplantation recurrent steatosis occur in majority of patients, although cirrhosis has been reported to develop in only 5%.

Hepatic steatosis in donor graft is common when the potential cadaveric donor liver having one third to one half of steatosis[64] grafts with less than 30% steatosis are acceptable for use, when the fat is more than 60%, grafts are generally considered unacceptable. Those with an (30% to 60%) intermediate degree of steatosis are evaluated on a case by case and center dependent basis.

Expert pathologist consultation regarding the liver biopsy prior to harvesting the organ for transplantation can be useful for determining donor acceptability.

ASSOCIATION BETWEEN HYPOTHYROIDISM & NAFLD

According to various studies there is growing data about higher prevalence of thyroid dysfunction in the form of subclinical hypothyroidism or overt hypothyroidism among the patient with NAFLD / NASH. The prevalence of hypothyroidism was reported to range from 15.2% to 36.3% among patient with NAFLD / NASH. Several studies that used healthy controls showed a significantly higher prevalence of hypothyroidism in patients with NAFLD / NASH compared to the control group. Several studies demonstrated that hypothyroidism is an independent risk factor for NAFLD. This indicates that hypothyroidism may directly result in NAFLD. Irrespective of other metabolic risk factors considering the results of these studies hypothyroidism may be added to

risk factors of NAFLD / NASH. Chung et al, in their population based study, evaluated a relatively, large numbers of healthy individuals and showed that prevalence of NAFLD plus elevated aminotransferase (ALT) was higher in patient with hypothyroidism.[65]

In increased serum ALT level is a surrogate biomarker for NAFLD in the absence of other causes of liver diseases and an indicator for the development of diabetes, cardiovascular disease and long term adverse complications from metabolic syndrome. Therefore study confirms the association between the severity of NAFLD and hypothyroidism.

Pagadala et all[66] reported that hypothyroidism was more common in patients with NASH compared to patient with NAFLD. This finding remained statistically significant after adjusting for other variables including age, diabetes, dyslipidemia and hypertension but not gender. This study which used liver biopsy and the NAFLD activity score to distinguish NASH from NAFLD, provides additional evidence for the association between the severities of liver fatty infiltration and hypothyroidism. Carulli et al[67] reported that an increased serum TSH level is on independent risk factors for NASH compared to patient with NAFLD.

While the underlying pathophysiology of the association between hypothyroidism and NAFLD is still not clear, several mechanism have been proposed. The role of adipocytokines in NAFLD has been

established previously, and some studies aimed to find a relationship between hypothyroidism and adipocytokines to clarify the mechanism of thyroid dysfunction and NAFLD. These studies failed to find an association between serum levels of adiponectin in hypothyroidism.[68] However, results of these studies were controversial for visfatin an adipocytokine involved in energy homeostasis.[69] An increased level of leptin has been identified in patients with hypothyroidism, and it may be responsible for the development of NAFLD / NASH. Leptin is an adipocytokine involved in the regulation of appetite with an increased level seen in cases of obesity, which can induce collagen synthesis in the liver and promotes hepatic insulin resistance.[70]

Patients with NAFLD / NASH have abnormal lipid profile notable for elevated low density lipoproteins, cholesterol and triglycerides levels.[71] Thyroid hormones induce their effects on lipid metabolism via thyroid hormone receptor Beta, which is expressed in liver[72]. In the hepatocytes thyroid hormone receptor activation results in reduction of body weight and fat as well as decrease in cholesterol and triglyceride levels. Cable et al[73] showed that liver steatosis will reduce after treatment of animal models with liver targeted thyroid hormone receptor agonist. Furthermore, hypothyroidism and elevated TSH result in diminished hepatic lipoprotein lipase activity and cause elevated serum triglyceride levels.[74]

The role of Fibroblast Growth Factor 21 (FGF 21) has been recently proposed in NAFLD / NASH[75]. FGF 21 induces glucose uptake in mouse and human adipocytes, which can improve glucose homeostasis after administration to obese mice. Increased serum levels of FGF-21 in NAFLD have been described in several human studies indicating that a relative FGF-21 resistance in these patients. An increased plasma levels of FGF-21 in patients with hypothyroidism has been observed in recent studies by Lee and coworkers.[76]

The precise mechanism by which FGF 21 pathway involved in NAFLD remaining to be elucidate.

The other theory is based on hepatic damage through mitochondrial dysfunction, oxidative stress and reactive oxygen species (ROS) production. Oxidative stress is a phenomenon in which a redox imbalance between prooxidants and antioxidants occurs in favor of prooxidants.[77]The principle organelle for oxidative reaction like Beta oxidation is mitochondria, and they are a main source of ROS.[78] Free Fatty acids (FFA) undergo beta oxidation in mitochondria under physiologic conditions. When the FFA accumulated in excess within the hepatocytes, there is excessive oxidation of FFA apart from mitochondria also occur in microsomes and peroxisomes leading to over production of ROS.[79] ROS activates lipid peroxidation that is accompanied by activation of kupffer cells and hepatic satellite cells[80]. Kupffer cells can

induce the secretion of inflammatory cytokines like tumour necrosis factor alpha and transforming growth factor Beta that both activate hepatic stellate cells and promote fibrosis.[81,82] Previous studies described increased markers of oxidative stress such as serum malonodialdehyde in hypothyroidism. Elevated serum markers of oxidative stress have been observed in hypothyroidism associated with Hashimoto's thyroiditis.

MATERIALS AND METHODS

MATERIALS AND METHODS

Study design:

Cross sectional study

Setting:

Patients with Hypothyroidism are enrolled for the study at Institute of Internal medicine, Madras Medical College & Rajiv Gandhi Government General Hospital.

Sample size determination:

χ^2 tests - Goodness-of-fit tests: Contingency tables

Analysis: A priori: Compute required sample size

Input:	Effect size w	= 0.431
	α err prob	= 0.099
	Power (1-β err prob)	= 0.915
	Df	= 1
Output:	Noncentrality parameter λ	=9.288050
	Critical χ^2	= 2.721580
	Total sample size	= 50
	Actual power	= 0.918931

Sample size:

50 patients with Hypothyroidism are enrolled for the study at Institute of Internal medicine, Madras Medical College & Rajiv Gandhi Government General Hospital. Informed consent was obtained from the patients.

Inclusion Criteria:

Patients with Hypothyroidism and aged more than 18 years.

Exclusion Criteria:

Those patients with BMI more than 30, Diabetes Mellitus, Dyslipidemia, Alcohol intake more than 20g/day and also patients with Hepatitis B, Hepatitis C and HIV Positive were excluded from the study.

Procedure:

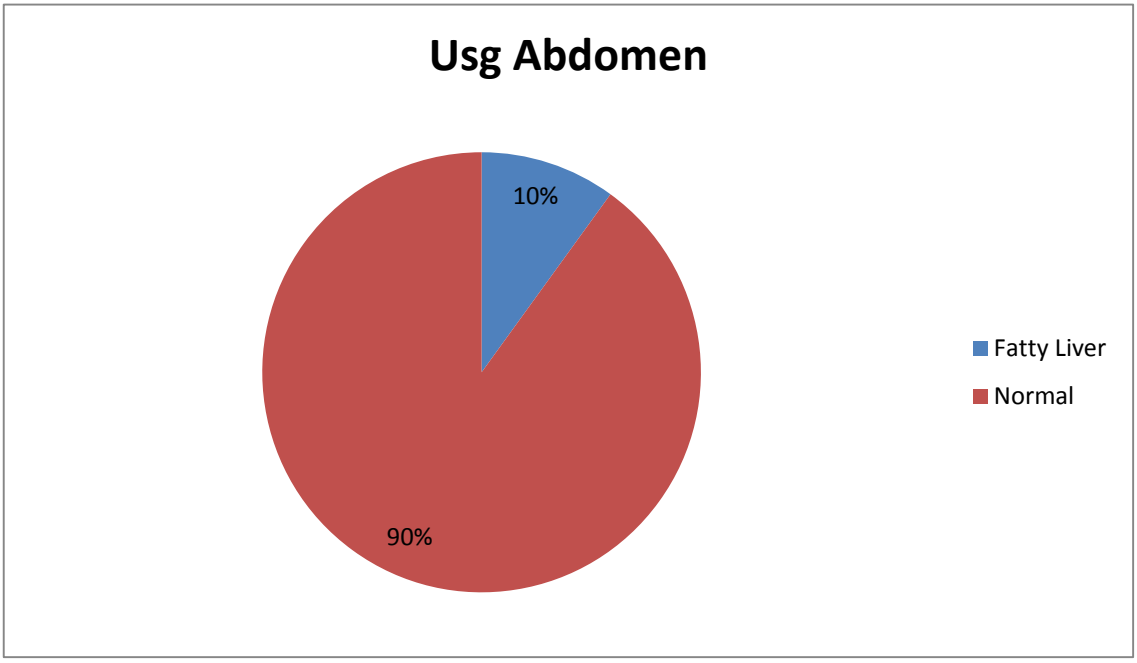
A questionnaire was prepared which include symptoms like weight gain, fatigue, constipation, cold intolerance, dry skin, hair changes, voice changes, menstrual irregularities were asked. Past medical, surgical history & personal history like alcohol intake and drug history were elicited. Physical examination was conducted which includes the vitals, height, weight, BMI, head to foot examination for Hypothyroidism. Systemic examination was conducted which includes examination of CVS, RS, Abdomen and CNS. Presence / Absence of hepatomegaly were

in abdominal examination. Investigation like complete blood count, RBS, Renal & Liver function test, fasting lipid profile, coagulation profile, viral markers, CRP, TFT (Free T3, Free T4 & TSH), USG Abdomen were done for all the 50 patients. Those who showed positive for fatty liver were subjected to fibroscan to study the stage of NAFLD.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

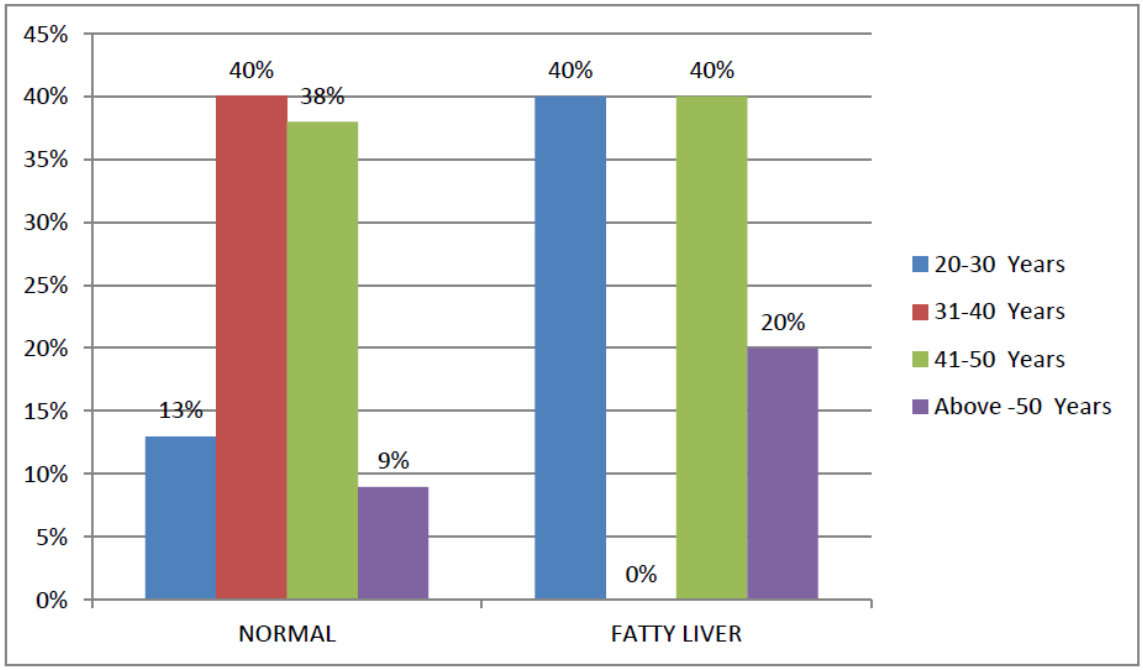
USG_ABDOMEN					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	FATTY LIVER	5	10.0	10.0	10.0
	NORMAL	45	90.0	90.0	100.0
	Total	50	100.0	100.0	



FIBRO_SCANkpa					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid		45	90.0	90.0	90.0
	4.7(F0)	1	2.0	2.0	92.0
	4.9(F0)	1	2.0	2.0	94.0
	5.1(F0)	1	2.0	2.0	96.0
	6.5(F1)	1	2.0	2.0	98.0
	6.9(F1)	1	2.0	2.0	100.0
	Total	50	100.0	100.0	

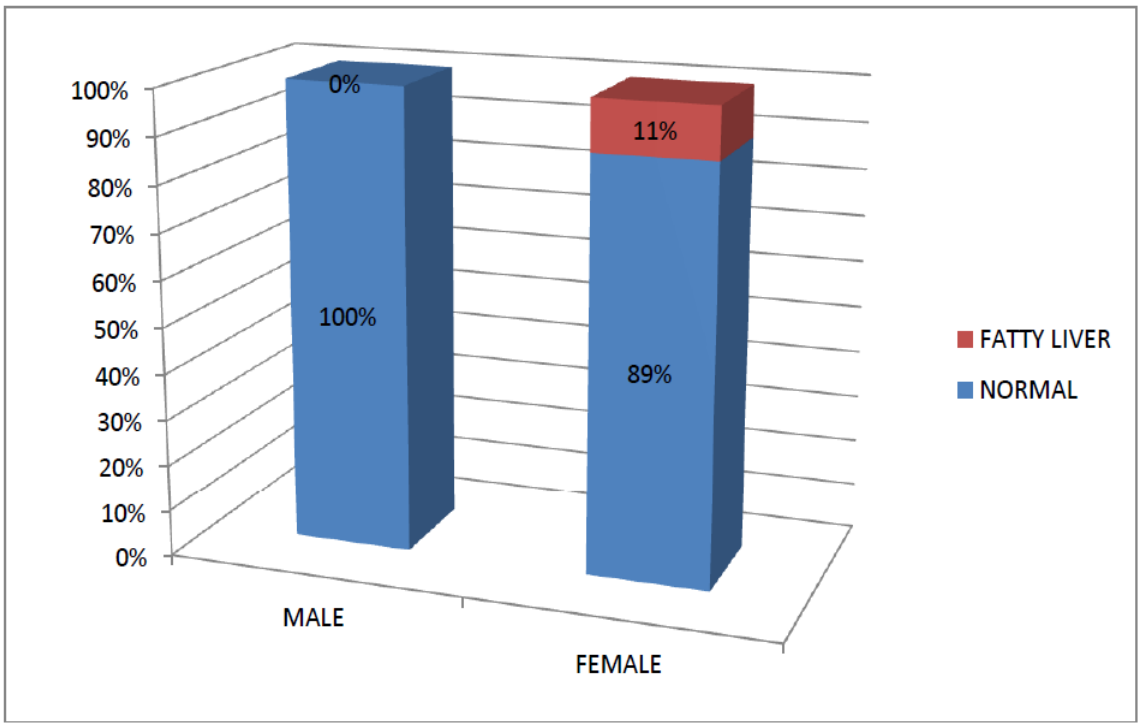
Crosstab					
			USG_ABDOMEN		Total
			NORMAL	FATTY LIVER	
age_group	20-30 Years	Count	6	2	8
		% within USG_ABDOMEN	13.3%	40.0%	16.0%
	31-40 Years	Count	18	0	18
		% within USG_ABDOMEN	40.0%	0.0%	36.0%
	41-50 Years	Count	17	2	19
		% within USG_ABDOMEN	37.8%	40.0%	38.0%
	Above -50 Years	Count	4	1	5
		% within USG_ABDOMEN	8.9%	20.0%	10.0%
Total		Count	45	5	50
		% within USG_ABDOMEN	100.0%	100.0%	100.0%

Pearson Chi-Square=4.561 p=0.207



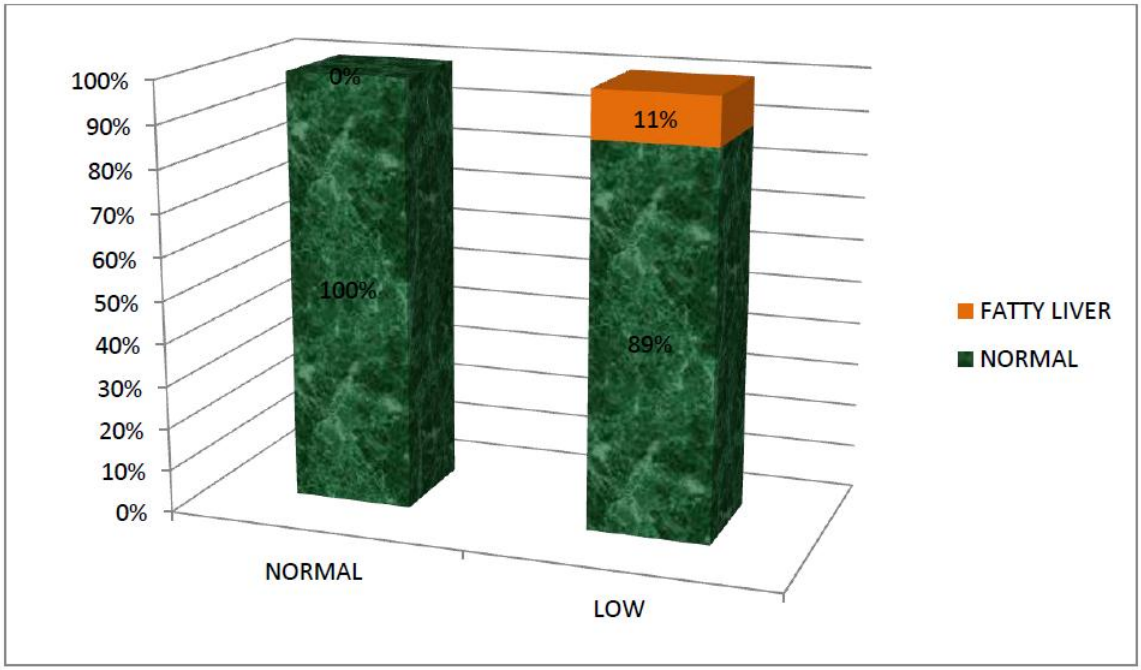
Crosstab					
			USG_ABDOMEN		Total
			NORMAL	FATTY LIVER	
SEX	Male	Count	4	0	4
		% within SEX	100.0%	0.0%	8.0%
	Female	Count	41	5	46
		% within SEX	89.1%	10.9%	92.0%
Total		Count	45	5	50
		% within SEX	100.0%	100.0%	100.0%

Pearson Chi-Square=0.483 p=0.487



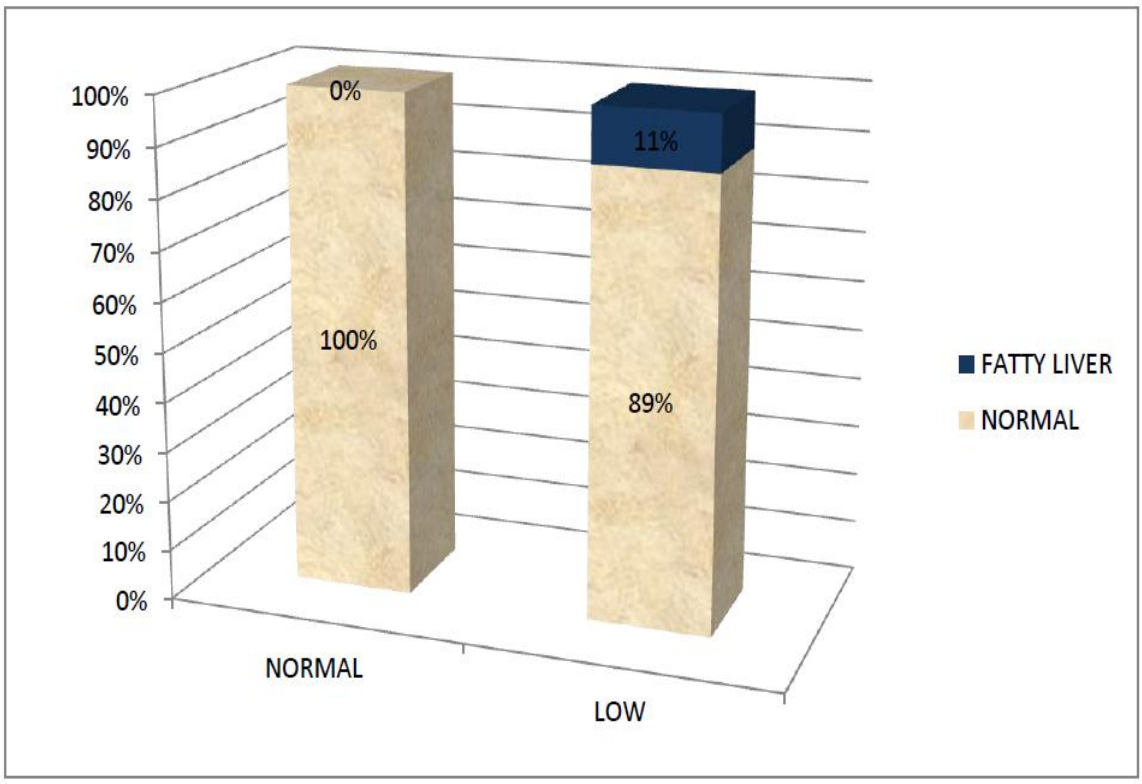
Crosstab					
			USG_ABDOMEN		Total
			FATTY LIVER	NORMAL	
t3_group	Normal	Count	0	6	6
		% within T3	0.0%	100.0%	100.0%
	Low	Count	5	39	44
		% within T3	11.4%	88.7%	100.0%
Total		Count	5	45	50
		% within T3	10.0%	90.0%	100.0%

Pearson Chi-Square=0.758 p=0.384



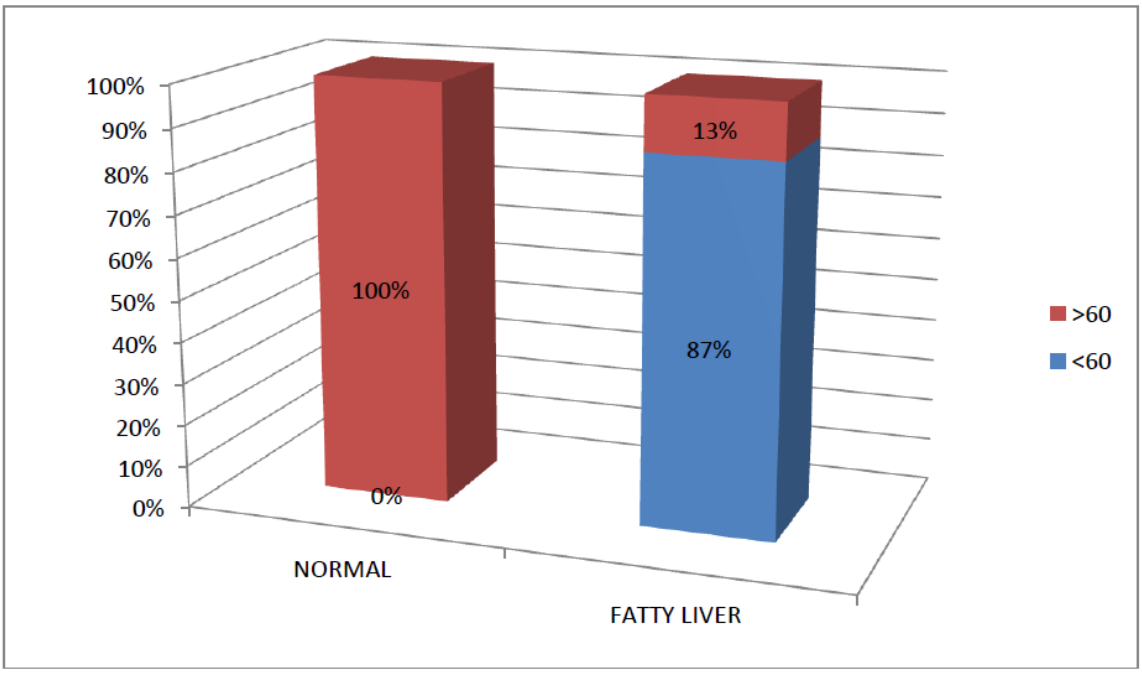
Crosstab					
			USG_ABDOMEN		Total
			FATTY LIVER	NORMAL	
t4_group	Normal	Count	0	6	6
		% within T4	0.0%	100.0%	100.0%
	Low	Count	5	39	44
		% within T4	11.4%	88.7%	100.0%
Total		Count	5	45	50
		% within T4	10.0%	90.0%	100.0%

Pearson Chi-Square=0.758 p=0.384



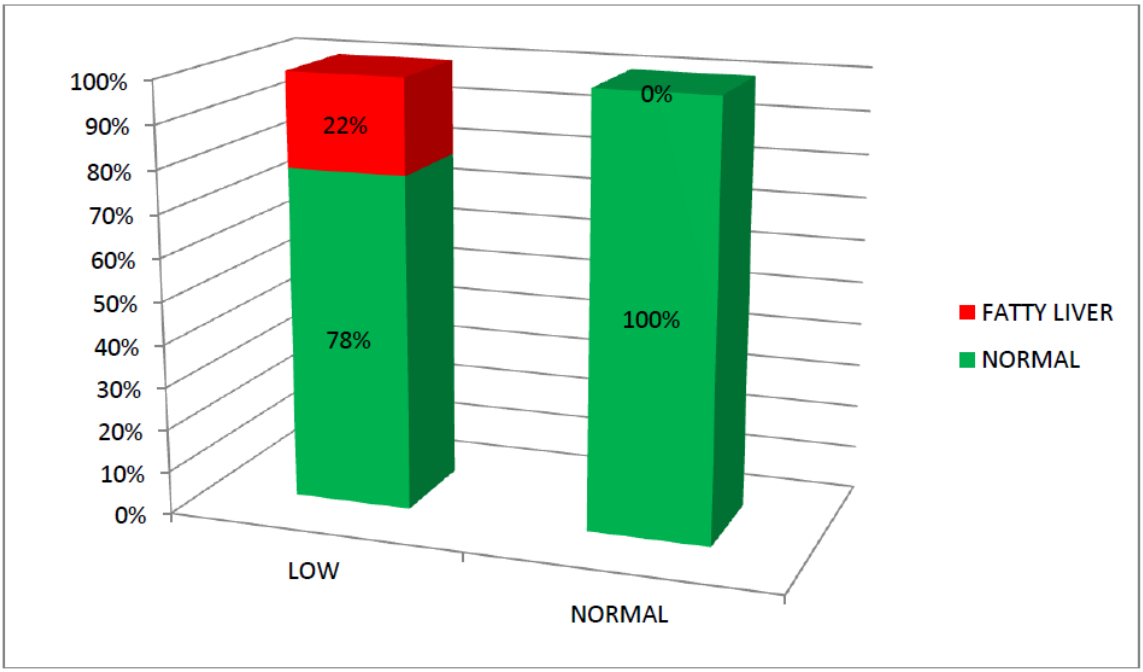
Crosstab					
			USG_ABDOMEN		Total
			FATTY LIVER	NORMAL	
tsh_group	<60	Count	0	39	39
		% within USG_ABDOMEN	0.0%	86.7%	78.0%
	>60	Count	5	6	11
		% within USG_ABDOMEN	100.0%	13.3%	22.0%
Total		Count	5	45	50
		% within USG_ABDOMEN	100.0%	100.0%	100.0%

Pearson Chi-Square=19.697** p<0.001



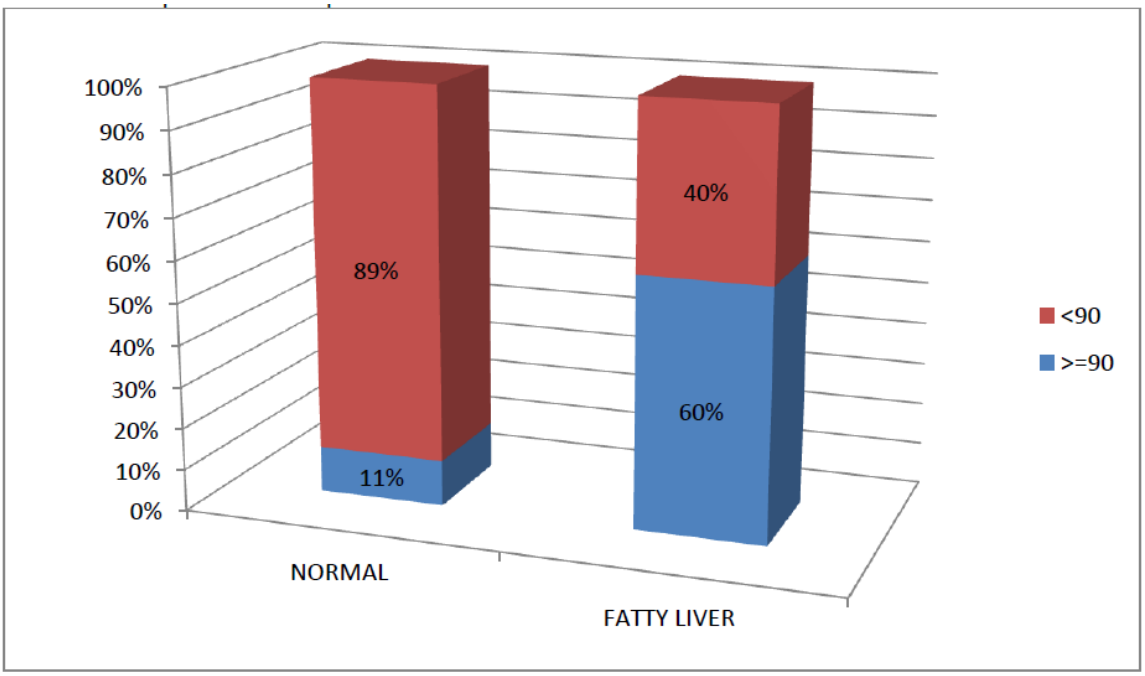
Crosstab					
			USG_ABDOMEN		Total
			FATTY LIVER	NORMAL	
hb_group	Low	Count	5	18	23
		% within HB GROUP	21.7%	78.3%	100.0%
	Normal	Count	0	27	27
		% within HB GROUP	0.0%	100.0%	100.0%
Total		Count	5	45	50
		% within HB GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=6.522** p=0.011

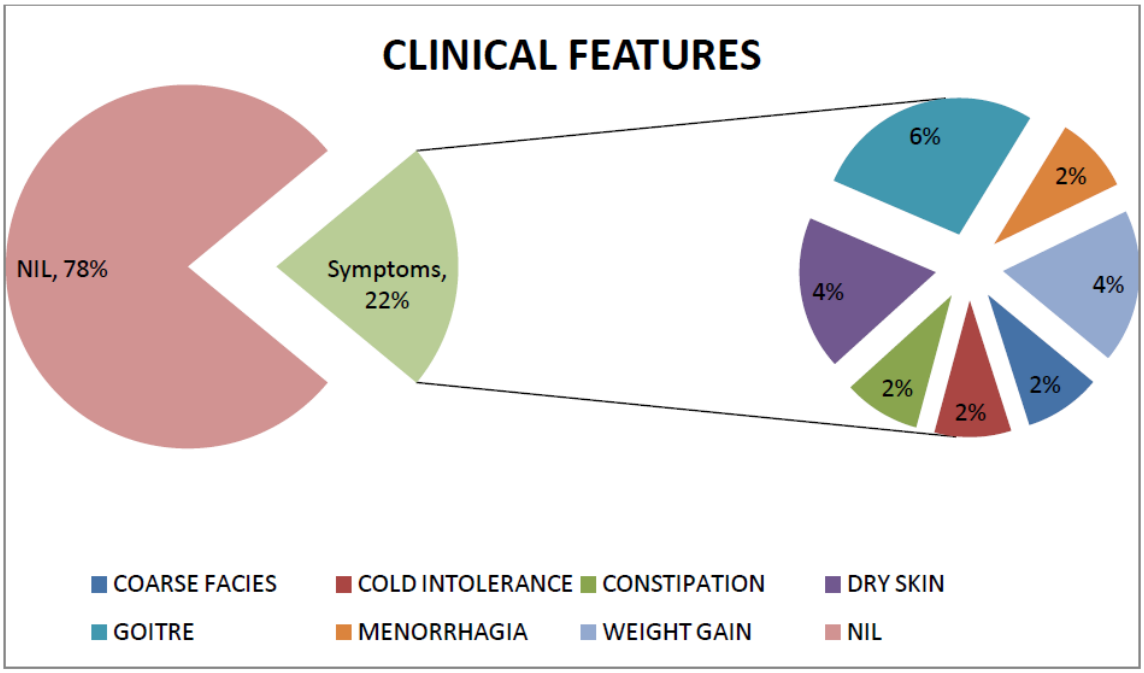


Crosstab					
			USG_ABDOMEN		Total
			FATTY LIVER	NORMAL	
diastolic	>=90	Count	3	5	8
		% within USG_ABDOMEN	60.0%	11.1%	16.0%
	<90	Count	2	40	42
		% within USG_ABDOMEN	40.0%	88.9%	84.0%
Total		Count	5	45	50
		% within USG_ABDOMEN	100.0%	100.0%	100.0%

Pearson Chi-Square=8.003 ** p=0.005



CLINICAL_FEATURES			
		Frequency	Percent
Valid	COARSE FACIES	1	2.0
	COLD INTOLERANCE	1	2.0
	CONSTIPATION	1	2.0
	DRY SKIN	2	4.0
	GOITRE	3	6.0
	MENORRHAGIA	1	2.0
	NIL	39	78.0
	WEIGHT GAIN	2	4.0
	Total	50	100.0



	Statistics								
		95% Confidence Interval for Mean							
	Mean	Lower Bound	Upper Bound	5% Trimmed Mean	Median	Variance	Std. Deviation	Minimum	Maximum
AGEyears	40.64	38.30	42.98	40.33	40.00	67.66	8.23	27.00	62.00
FREE_T3pmoll	2.55	2.40	2.69	2.51	2.40	0.26	0.51	1.60	3.90
FREE_T4ngdl	0.58	0.50	0.66	0.56	0.50	0.08	0.28	0.20	1.40
TSHIUml	47.06	41.11	53.01	45.58	42.86	438.20	20.93	18.48	102.78
Hbgmdl	11.58	11.16	11.99	11.60	12.30	2.13	1.46	9.00	13.80
T#BILIRUBINmgdl	0.69	0.67	0.72	0.69	0.70	0.01	0.09	0.50	0.90
D#BILIRUBINmgdl	0.30	0.28	0.31	0.30	0.30	0.00	0.06	0.20	0.40
ASTIUL	30.24	29.85	30.63	30.29	30.00	1.86	1.36	27.00	32.00
ALTIUL	33.10	32.74	33.46	33.11	33.00	1.60	1.27	30.00	36.00
ALPIUL	95.24	93.67	96.81	95.12	95.00	30.39	5.51	85.00	108.00
Sr#ALBUMINgmdl	4.47	4.41	4.53	4.47	4.45	0.04	0.21	4.00	4.90
PTsec	13.42	13.17	13.67	13.41	13.00	0.78	0.88	12.00	15.00
INR	0.89	0.86	0.92	0.89	0.90	0.01	0.12	0.70	1.10
CRPmglit	3.65	3.50	3.81	3.68	3.80	0.30	0.55	2.20	4.40

INDEPENDENT T TEST						T VALUE	P VALUE
USG		N	Mean	Std. Deviation	Std. Error Mean		
AGEyears	NORMAL	45	40.56	7.53	1.12	0.216	0.83
	FATTY LIVER	5	41.40	14.29	6.39		
FREE_T3pmoll	NORMAL	45	2.59	0.51	0.08	1.735	.089
	FATTY LIVER	5	2.18	0.38	0.17		
FREE_T4ngdl	NORMAL	45	0.61	0.28	0.04	2.080*	.043
	FATTY LIVER	5	0.34	0.11	0.05		
TSHIUml	NORMAL	45	41.44	12.79	1.91	9.686**	P<0.0001
	FATTY LIVER	5	97.62	4.09	1.83		
Hbgmdl	NORMAL	45	11.82	1.32	0.20	4.171**	P<0.0001
	FATTY LIVER	5	9.34	0.31	0.14		
T#BILIRUBINmgdl	NORMAL	45	0.69	0.09	0.01	0.297	.768
	FATTY LIVER	5	0.68	0.13	0.06		
D#BILIRUBINmgdl	NORMAL	45	0.30	0.06	0.01	1.417	.163
	FATTY LIVER	5	0.26	0.09	0.04		
ASTIUL	NORMAL	45	30.16	1.38	0.21	-1.324	.192
	FATTY LIVER	5	31.00	1.00	0.45		
ALTIUL	NORMAL	45	33.09	1.31	0.20	-0.184	.854
	FATTY LIVER	5	33.20	0.84	0.37		
ALPIUL	NORMAL	45	95.80	5.34	0.80	2.242*	.030
	FATTY LIVER	5	90.20	4.82	2.15		
Sr#ALBUMINgmdl	NORMAL	45	4.49	0.19	0.03	2.181*	.034
	FATTY LIVER	5	4.28	0.31	0.14		
PTsec	NORMAL	45	13.47	0.89	0.13	1.125	.266
	FATTY LIVER	5	13.00	0.71	0.32		
INR	NORMAL	45	0.89	0.12	0.02	-0.586	.561
	FATTY LIVER	5	0.92	0.11	0.05		
CRPmglit	NORMAL	45	3.64	0.55	0.08	-0.714	.479
	FATTY LIVER	5	3.82	0.48	0.21		

*P<0.05,**P<0.001

DISCUSSION

DISCUSSION

A cross sectional study was conducted at our Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital for a period of 6 month from March 2017 to August 2017.

50 patients with Hypothyroidism were chosen from Endocrinology department based on the inclusion and exclusion criteria as mentioned above.

In this study 10% of patients showed fatty liver. Fibroscan was done for them, it has showed no significant fibrosis.

Among the 10% of the patient with fatty liver 40% were in the age group of 20 to 30 years, 40% were in the age group of 41 to 50 years and the remaining 20% were above 50 years. Pearson Chi square was 4.561 and P value showed 0.207 which is not significant. So there is no significance between age and fatty liver in patients suffering from Hypothyroidism.

Fatty liver was observed in 11% of female patients but none of the male patients showed fatty liver. Pearson Chi Square was 0.483 and P value showed 0.487 which is not significant. So there is no significant relationship between sex and NAFLD in patients with Hypothyroidism.

T3 and T4 level in Hypothyroid patients with fatty liver were compared with Hypothyroid patients with normal liver in this study. Around 11% of patients with low free T3 and free T4 had fatty liver and none of the patients with normal free T3 and free T4 showed fatty liver in our study. Pearson Chi Square was 0.758 and P value showed 0.384 for both T3 and T4, which is not significant. So there is no significance between T3 & T4 level and fatty liver in patients with Hypothyroidism.

From this study, it has been observed that there is high incidence of fatty liver in patients whose TSH level more than 60. Around 87% patients with fatty liver had TSH more than 60.The value was calculated for the relationship which came to be less than 0.001 which is significant.

Hypothyroid patients with anaemia had higher incidence of fatty liver in our study. Around 22% of patients with low haemoglobin had fatty liver and none of the patients with normal haemoglobin showed fatty liver. Pearson Chi Square was 6.522 and P value was 0.011 which is significant. So there is a significant relationship between haemoglobin level and NAFLD in patients with Hypothyroidism.

Hypothyroid patients diastolic BP of more than or equal to 90 showed fatty liver more than that of Hypothyroid patients with diastolic BP of less than 90. Around 60% patients with fatty liver had diastolic BP more than or equal to 90. The value was calculated for the relationship which came to be less than 0.005 which is significant.

LIMITATIONS OF STUDY

LIMITATIONS OF THE STUDY

- We found that in our study there were some limitations with the sample size which precluded us from getting statistical significance with regard to certain variables with NAFLD.

- Effects of the thyroxine medications have not been included in the assessment.

CONCLUSION

CONCLUSION

- Hypothyroidism is a independent risk factor for NAFLD. So NAFLD screening is mandatory for all the patients with Hypothyroidism.

- Early treatment of Hypothyroidism with thyroxine may reduce the risk of NAFLD and its potential complications. An extensive study is needed to find the effects of thyroid hormone replacement therapy in patients with Hypothyroidism for preventing NAFLD.

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BIBLIOGRAPHY

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ANNEXURES

PROFORMA

Patient's Name : Date :

Age/sex : Serial No.

Address :

Contact Number :

Occupation :

OP/ IP Number :

SYMPTOMS

Weight gain

Fatigue

Constipation

Cold intolerance

Dry skin

Hair changes

Voice change

Menstrual irregularities

PAST MEDICAL AND SURGICAL HISTORY

DM/ SHT/ CAD / CKD/ others

SUBSTANCE USE HISTORY

Alcohol use :

Others :

TREATMENT HISTORY :

GENERAL EXAMINATION :

Pallor

Icterus

Pedal edema

Clubbing

Peripheral lymphadenopathy

Goitre

WEIGHT :

HEIGHT :

BMI :

VITAL SIGNS :

BP :

PR :

RR :

Temperature :

CVS EXAMINATION :

RS EXAMINATION :

ABDOMEN EXAMINATION :

CNS EXAMINATION :

INVESTIGATIONS :

CBC :

TC :

DC :

Hb :

RBC Count :

Platelet count :

RFT :

Blood urea :

Serum creatinine :

LFT :

Total bilirubin :

Direct bilirubin :

AST:

ALT :

ALP :

Total protein :

Serum albumin :

TFT :

Free T3 :

Free T4 :

Serum TSH :

RBS :

Fasting Lipid Profile :

Serum CRP :

Viral markers :

Anti HBsAg :

Anti HCV :

HIV Elisa :

Ultrasound Abdomen :

Fibroscan :

ETHICAL COMMITTEE APPROVAL

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.A. Dinesh
Post Graduate in M.D.(General Medicine)
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.A.Dinesh,

The Institutional Ethics Committee has considered your request and approved your study titled **"RELATION BETWEEN HYPOTHYROIDISM AND NAFLD (NON ALCOHOLIC FATTY LIVER DISEASE) " - NO.12022017**

The following members of Ethics Committee were present in the meeting hold on **07.02.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.S.Suresh, MS., Prof.of Surgery, MMC, Ch-3	: Member
5.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
6.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
7.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
8.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
9.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
10.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
11.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE.
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

PLAGIARISM SCREENSHOT

Urkund Analysis Result

Analysed Document: HYPOTHYROIDISM1.doc (D31188247)
Submitted: 10/10/2017 3:56:00 PM
Submitted By: dinesharunagiri87@gmail.com
Significance: 2 %

Sources included in the report:

Apurva Nagesh Sharma.docx (D16699630)
ezhil intro.doc (D31018840)
https://en.wikipedia.org/wiki/Subclinical_hypothyroidism
http://www.aafp.org/afp/2005/1015/p1517.html

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled "**RELATION BETWEEN HYPOTHYROIDISM AND NON-ALCOHOLIC FATTY LIVER DISEASE**" of the candidate DR.A.DINESH with registration Number 201511003 for the award of M.D in the branch of GENERAL MEDICINE. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 2 percentage of plagiarism in the dissertation.

Guide & Supervisor sign with Seal

INFORMATION SHEET

We are conducting a study on **"RELATION BETWEEN HYPOTHYROIDISM AND NAFLD (NON-ALCOHOLIC FATTY LIVER DISEASE)"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to identify the relation between hypothyroidism and NAFLD. We are selecting certain cases and if you are found eligible, we may perform extra tests and special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Signature of Participant

Date :

Place :

PATIENT CONSENT FORM

Study Detail	:	**RELATION BETWEEN HYPOTHYROIDISM AND NAFLD (NON-ALCOHOLIC FATTY LIVER DISEASE)**
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age/sex	:	
Identification Number	:	

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction.	☐
I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.	☐
I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released	☐

to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.	
I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.	☐
I hereby consent to participate in this study.	☐
I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests.	☐

Signature / thumb impression of patient Signature of Investigator

Patient's Name and Address

NORMAL REFERENCE VALUES

Free T3	-	3.1 to 6.8 pmol/L
Free T4	-	0.93 to 1.7 ng/dl
TSH	-	0.5 to 5.0 microIU/ml
Haemoglobin:		
Males	-	13.3 to 16.2 g/dl
Females	-	12 to 15.8 g/dl
T.Bilirubin	-	0.3 to 1.3 mg/dl
D.Bilirubin	-	0.1 to 0.4 mg/dl
AST	-	15 to 40 IU/L
ALT	-	15 to 40 IU/L
ALP	-	40 to 140 IU/L
Albumin	-	3.5 to 5.0 g/dl
Prothrombin Time	-	12 to 15.4 seconds
INR	-	0.7 to 1.3
CRP	-	Less than 5 mg/L

MASTER CHART

S.NO	AGE(years)	SEX	CLINICAL FEATURES	BP(mm hg)	FREE T3(pmol/l)	FREE T4(ng/dl)	TSH(IU/ml)	Hb(gm/dl)	T.BILIRUBIN(mg/dl)	D.BILIRUBIN(mg/dl)	AST(IU/L)	ALT(IU/L)	ALP(IU/L)	Sr.ALBUMIN(gm/dl)	PT(sec)	INR	CRP(mg/liť)	USG ABDOMEN	FIBRO SCAN(kpa)
1	47	F	DRY SKIN	120/94	2.2	0.4	92.13	9	0.6	0.2	32	34	96	4.1	13	0.9	3.7	FATTY LIVER	6.5(F1)
2	29	F	NIL	120/80	2.4	0.4	70.12	10.2	0.7	0.3	30	32	98	4.3	14	1.1	3.2	NORMAL	
3	30	F	NIL	120/80	2.6	0.6	49.11	9.3	0.8	0.3	29	31	92	4.2	13	1	3.8	NORMAL	
4	40	F	NIL	120/70	2.8	0.7	60.12	11.5	0.6	0.3	32	35	102	4.1	15	1.1	4.2	NORMAL	
5	44	F	NIL	110/90	2.6	0.4	50.11	12	0.7	0.4	30	33	106	4.4	14	0.8	4	NORMAL	
6	47	F	NIL	110/70	2.4	0.5	48.41	12.3	0.8	0.3	29	32	97	4.2	13	0.9	2.9	NORMAL	
7	42	F	NIL	110/70	2.2	0.6	60.52	12	0.7	0.3	28	31	94	4.1	14	1	4.4	NORMAL	
8	30	F	NIL	120/70	2.7	0.6	61.16	11.5	0.8	0.3	32	34	102	4.4	13	1.1	3.2	NORMAL	
9	42	F	GOITRE	120/96	2.1	0.3	102.78	9.2	0.8	0.3	30	32	94	4.2	12	0.8	3.1	FATTY LIVER	6.9(F1)
10	30	F	NIL	110/80	2.7	0.6	60.13	11.8	0.6	0.2	31	33	99	4.4	13	0.9	2.8	NORMAL	
11	38	M	NIL	120/70	2.2	0.5	55.41	13.5	0.7	0.3	32	34	102	4.6	12	1.1	2.7	NORMAL	
12	37	F	NIL	126/70	2.1	0.4	28.12	12.5	0.8	0.3	30	33	98	4.4	13	1	2.2	NORMAL	
13	42	F	NIL	120/70	3.3	1.2	40.12	11.5	0.7	0.3	31	34	97	4.6	12	0.9	3.8	NORMAL	
14	38	F	NIL	124/74	2.1	0.5	50.11	12.3	0.6	0.2	30	34	103	4.4	13	0.8	4.2	NORMAL	
15	42	F	NIL	110/70	2.2	0.4	40.46	11.5	0.7	0.3	28	33	106	4.3	15	0.9	4	NORMAL	
16	40	F	NIL	130/92	2.3	0.5	30.61	12.5	0.8	0.4	32	36	108	4.6	14	0.8	3.3	NORMAL	
17	39	F	NIL	120/76	2.4	0.4	40.12	12.8	0.7	0.3	32	34	97	4.3	13	0.7	3.1	NORMAL	
18	48	F	NIL	110/80	2.4	0.5	32.14	12.6	0.6	0.3	29	32	99	4.6	14	0.8	2.9	NORMAL	
19	32	F	NIL	110/80	2.2	0.4	40.81	12.9	0.8	0.3	31	34	106	4.7	12	0.9	2.7	NORMAL	
20	29	F	GOITRE	120/90	2.4	0.3	96.09	9.5	0.7	0.2	31	33	86	4	13	0.9	4.3	FATTY LIVER	4.9(F0)
21	44	F	NIL	110/80	2.4	0.6	28.14	12.6	0.7	0.3	32	34	98	4.4	12	0.8	4	NORMAL	
22	32	F	NIL	120/70	2.3	0.4	32.12	12.8	0.8	0.4	29	33	96	4.6	13	0.7	3.8	NORMAL	
23	56	F	NIL	128/94	2.1	0.5	42.22	12.2	0.9	0.3	30	32	92	4.7	12	0.9	3.1	NORMAL	

24	40	F	NIL	110/80	3.8	1.3	20.91	12.5	0.8	0.3	28	30	90	4.8	13	1	3.7	NORMAL	
25	62	F	COARSE FACIES	130/94	2.6	0.5	96.8	9.2	0.8	0.4	30	33	90	4.3	14	0.9	4.2	FATTY LIVER	5.1(F0)
26	58	F	NIL	120/70	2.3	0.4	50.42	9.5	0.7	0.3	32	33	92	4.6	13	0.9	3.8	NORMAL	
27	43	F	NIL	120/90	2.4	0.6	46.12	12.3	0.6	0.2	31	34	88	4.6	14	0.8	4	NORMAL	
28	36	F	NIL	110/70	2.7	0.6	43.49	12.2	0.7	0.3	32	35	89	4.7	13	0.7	3.8	NORMAL	
29	27	F	NIL	110/70	2.4	0.5	30.14	12.4	0.6	0.2	32	36	88	4.6	14	1.1	4	NORMAL	
30	27	F	DRY SKIN	110/70	1.6	0.2	100.31	9.8	0.5	0.2	32	34	85	4.8	13	1.1	3.8	FATTY LIVER	4.7(F0)
31	42	F	NIL	110/74	3.8	1.3	30.36	9.6	0.6	0.3	30	33	92	4.9	12	0.9	3.7	NORMAL	
32	41	F	NIL	120/70	2.2	0.4	50.12	12.6	0.7	0.4	31	34	96	4.2	13	0.8	2.7	NORMAL	
33	48	F	NIL	120/80	3	0.3	56.14	12.7	0.8	0.3	29	32	92	4.4	14	0.7	4.3	NORMAL	
34	50	F	NIL	130/90	2.6	0.6	60.12	12.5	0.6	0.3	30	33	94	4.6	13	0.8	3.6	NORMAL	
35	46	M	NIL	120/70	2.1	0.4	46.41	13.2	0.7	0.3	32	34	87	4.4	14	0.9	2.9	NORMAL	
36	38	F	NIL	110/70	2.2	0.6	27.64	9.4	0.6	0.2	30	33	89	4.5	13	0.8	4.1	NORMAL	
37	36	F	NIL	130/80	3.8	1.4	22.71	9.5	0.7	0.4	29	32	92	4.6	14	0.9	4	NORMAL	
38	40	F	NIL	120/70	2.2	0.6	27.68	12.3	0.5	0.3	32	34	97	4.7	13	0.9	3.8	NORMAL	
39	57	F	NIL	120/80	2.4	0.4	43.92	12.5	0.7	0.3	30	33	96	4.3	15	0.8	3.7	NORMAL	
40	29	F	NIL	126/92	2.6	0.6	38.34	12.7	0.8	0.3	29	32	94	4.6	14	0.9	4.2	NORMAL	
41	49	F	NIL	110/80	2.4	0.3	40.12	12.6	0.6	0.3	27	30	96	4.7	13	1	3.9	NORMAL	
42	42	F	NIL	120/70	3.8	1.2	30.92	9.6	0.7	0.4	30	32	94	4.3	15	1.1	4	NORMAL	
43	40	F	NIL	124/92	2.4	0.6	21.96	9.4	0.8	0.3	29	32	101	4.5	14	1	4.2	NORMAL	
44	38	M	NIL	120/70	2.2	0.5	32.38	13.8	0.7	0.3	30	33	92	4.6	15	0.8	2.9	NORMAL	
45	35	F	NIL	110/70	2.3	0.5	30.14	12.5	0.6	0.3	31	34	98	4.3	13	0.9	3.5	NORMAL	
46	45	F	NIL	130/70	2.7	0.6	48.69	12.8	0.5	0.2	30	34	89	4.4	14	0.7	3.9	NORMAL	
47	36	F	NIL	120/70	2.6	0.5	40.12	9.5	0.6	0.3	29	33	92	4.6	15	0.9	4.3	NORMAL	
48	46	F	NIL	120/92	2.4	0.6	30.63	9.6	0.7	0.4	28	32	94	4.4	14	0.8	4	NORMAL	
49	51	M	NIL	120/76	2.8	0.6	56.71	13.3	0.8	0.3	29	33	98	4.7	13	0.7	4.2	NORMAL	
50	32	F	NIL	120/78	3.9	1.3	18.48	12.8	0.6	0.2	30	34	89	4.6	14	0.9	4.1	NORMAL	

NORMAL REFERENCE VALUES

Free T3	-	3.1 to 6.8 pmol/L
Free T4	-	0.93 to 1.7 ng/dl
TSH	-	0.5 to 5.0 microIU/ml
Haemoglobin:		
Males	-	13.3 to 16.2 g/dl
Females	-	12 to 15.8 g/dl
T.Bilirubin	-	0.3 to 1.3 mg/dl
D.Bilirubin	-	0.1 to 0.4 mg/dl
AST	-	15 to 40 IU/L
ALT	-	15 to 40 IU/L
ALP	-	40 to 140 IU/L
Albumin	-	3.5 to 5.0 g/dl
Prothrombin Time	-	12 to 15.4 seconds
INR	-	0.7 to 1.3
CRP	-	Less than 5 mg/L